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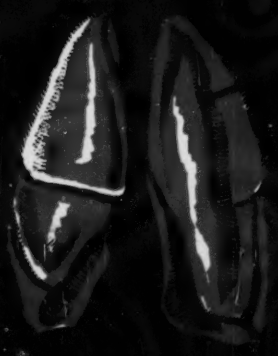

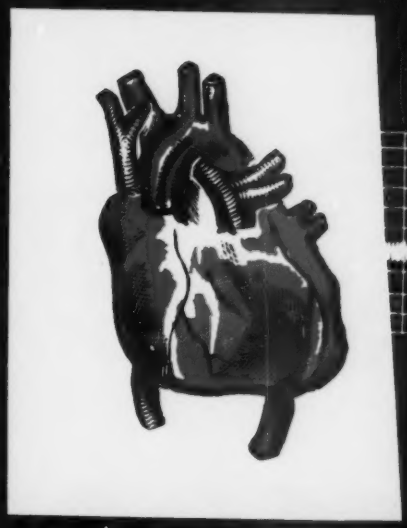

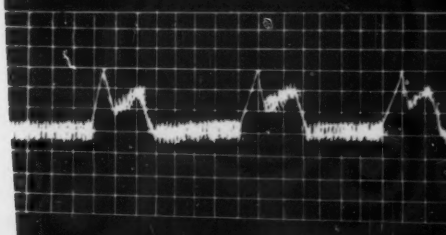

## CONGESTIVE HEART FAILURE

MICHIGAN HEART ASSOCIATION

*This number is composed of three sections, of which this is Section 1*

# IN EPILEPSY... PREREQUISITE FOR PARTICIPATION: THERAPY

**With the use of medications, epileptic students may be enabled to participate in many of the same activities as other students.[1]**

# REQUISITE FOR THERAPY: THE PARKE-DAVIS FAMILY OF ANTICONVULSANTS

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CELONTIN Kapseals (methsuximide, Parke-Davis) 0.3 Gm., bottles of 100.

**bibliography:** (1) Green, J. R., & Steelman, H. F.: Epileptic Seizures, Baltimore, Williams & Wilkins Company, 1956, p. 136. (2) Bray, P. F.: *Pediatrics* **23**:151, 1959. (3) Davidson, D. T., Jr., in Conn, H. F.: Current Therapy 1959, Philadelphia, W. B. Saunders Company, 1959, p. 512. (4) Smith, B., & Forster, F. M.: *Neurology* **4**:137, 1954. (5) Zimmerman, F. T.: *New York J. Med.* **55**:2338, 1955. (6) Lemere, F.: *Northwest Med.* **53**:482, 1954. (7) Perlstein, M. A.: *Pediat. Clin. North America*: **4**:1079 (Nov.) 1957. (8) Livingston, S., & Pauli, L.: *Pediatrics* **19**:614, 1957. (9) Carter, C. H., & Maley, M. C.: *Neurology* **7**:483, 1957. (10) Keith, H. M., & Rushton, J. G.: *Proc. Staff Meet. Mayo Clin.* **33**:105, 1958.

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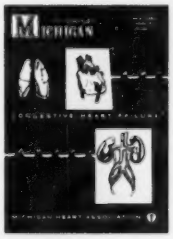


THE COVER . . . Heart associations across the nation plan this year to expand their educational effort for physicians on congestive heart failure. Future plans will include an education program stressing congestive heart failure and what can be done about it.

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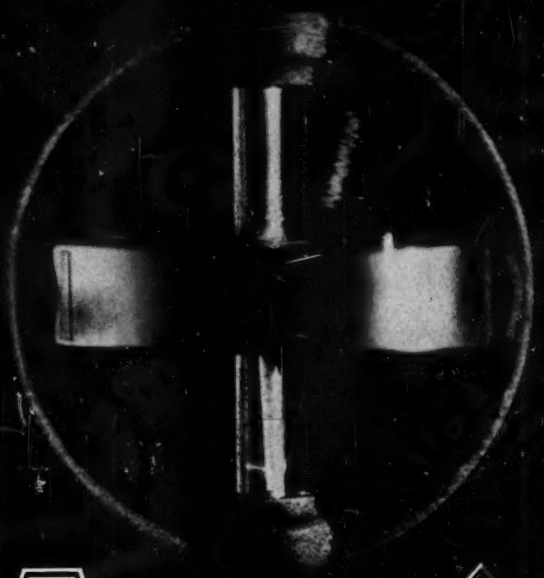

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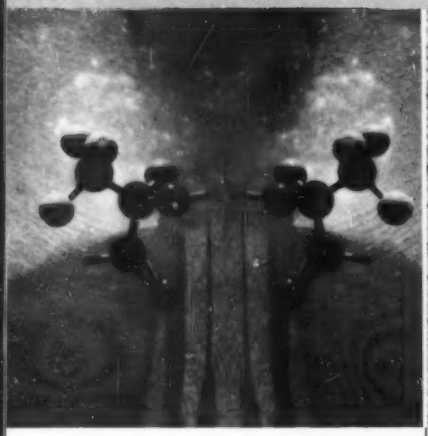

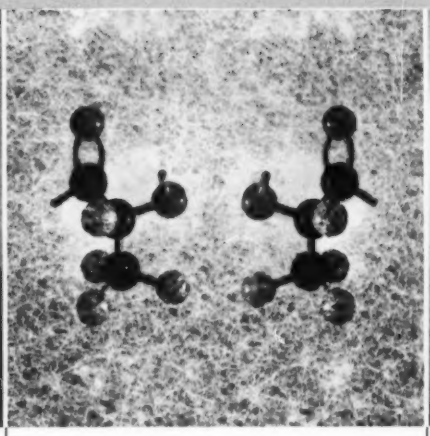

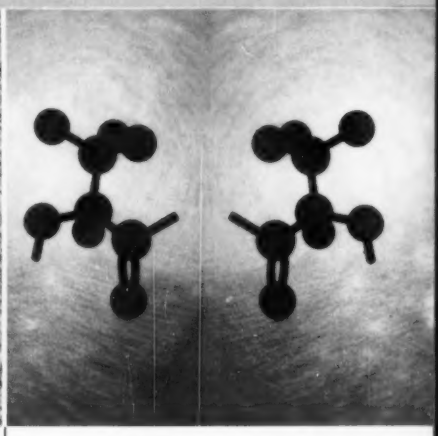

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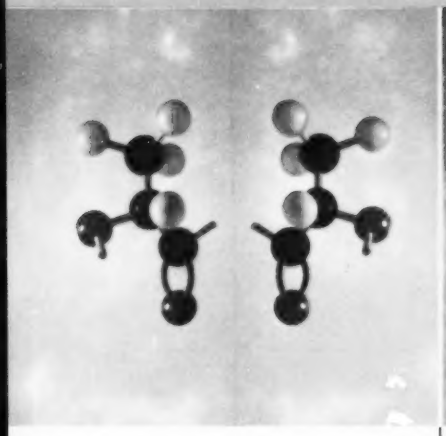
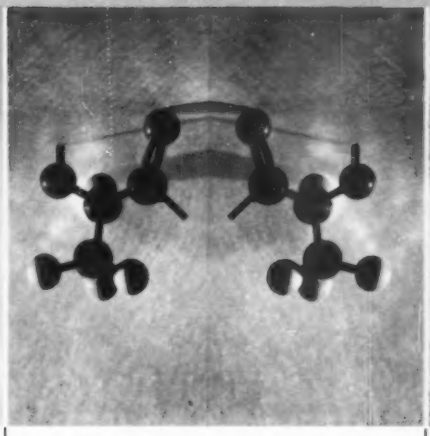
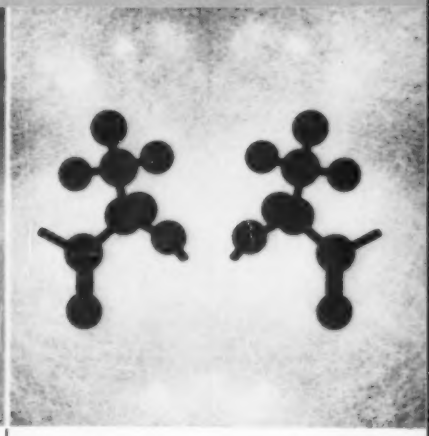






*ANTIBIOTIC ACTIVITY DIRECTLY PROPORTIONAL TO ORAL DOSE*

*REDUCED HAZARD OF SERIOUS ALLERGENICITY BY SAFER ORAL ROUTE*

*MANY STAPH STRAINS MORE SENSITIVE TO SYNCILLIN*

BRISTOL

# *ORIGIN OF A NEW SYNTHETIC PENICILLIN*

In March, 1957, Dr. John C. Sheehan of the Massachusetts Institute of Technology announced the total synthesis of penicillin from common raw materials, thus solving a problem which had baffled research workers for more than 15 years. Although total synthesis was not commercially practicable, this work, sponsored by Bristol Laboratories, made possible the subsequent synthesis of new penicillins not occurring in nature. Later scientists at Beecham Laboratories in England discovered that a key intermediate (6-aminopenicillanic acid) could be produced by a fermentation process. With these achievements, large scale production of synthetic penicillins became feasible.

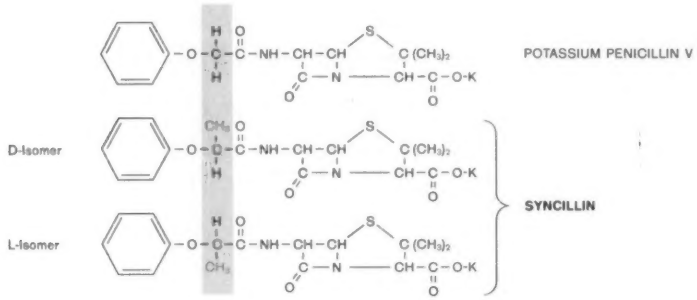
Organic chemists at Bristol then embarked upon an intensive program to develop better penicillins. Over five hundred were synthesized and underwent preliminary screening. Forty-six showed sufficient promise to warrant further investigation. Extensive microbiological, pharmacological, and clinical screening indicated that one compound, SYNCILLIN, had advantages of major importance over other penicillins.

SYNCILLIN is the N-acylation product of 6-aminopenicillanic acid and $\alpha$-phenoxypropionic acid (the phenylether of lactic acid). It is freely soluble in water and remarkably resistant to decomposition by acid. The acid stability of SYNCILLIN is equivalent to that of penicillin V at pH 2 and pH 3 at 37° C.[1]

# *SIGNIFICANCE OF MOLECULAR ASYMMETRY AND ISOMERIC COMPLEMENTARITY*

SYNCILLIN has a molecular configuration similar to penicillin V, but contains an additional $CH_3$ group so positioned as to render the adjacent carbon atom asymmetric. (In the formulae below, the added $CH_3$ group is shown in blue and the asymmetric carbon atom in red.) As a result, SYNCILLIN occurs as a mixture of two isomers.

Each isomer has been synthesized in essentially pure form and found to possess distinctive chemical and biological properties. The L-isomer is 2 to 17 times more active than the D-isomer against many of the organisms tested. As produced, SYNCILLIN is a mixture of the L-isomer and the D-isomer. As will be shown later, the antibiotic effect of the clinically available mixture, SYNCILLIN, is greater than either isomer alone against many organisms. This phenomenon is referred to here as *isomeric complementarity*.




# *SYNCILLIN*

*major therapeutic advantages accompany molecular asymmetry*

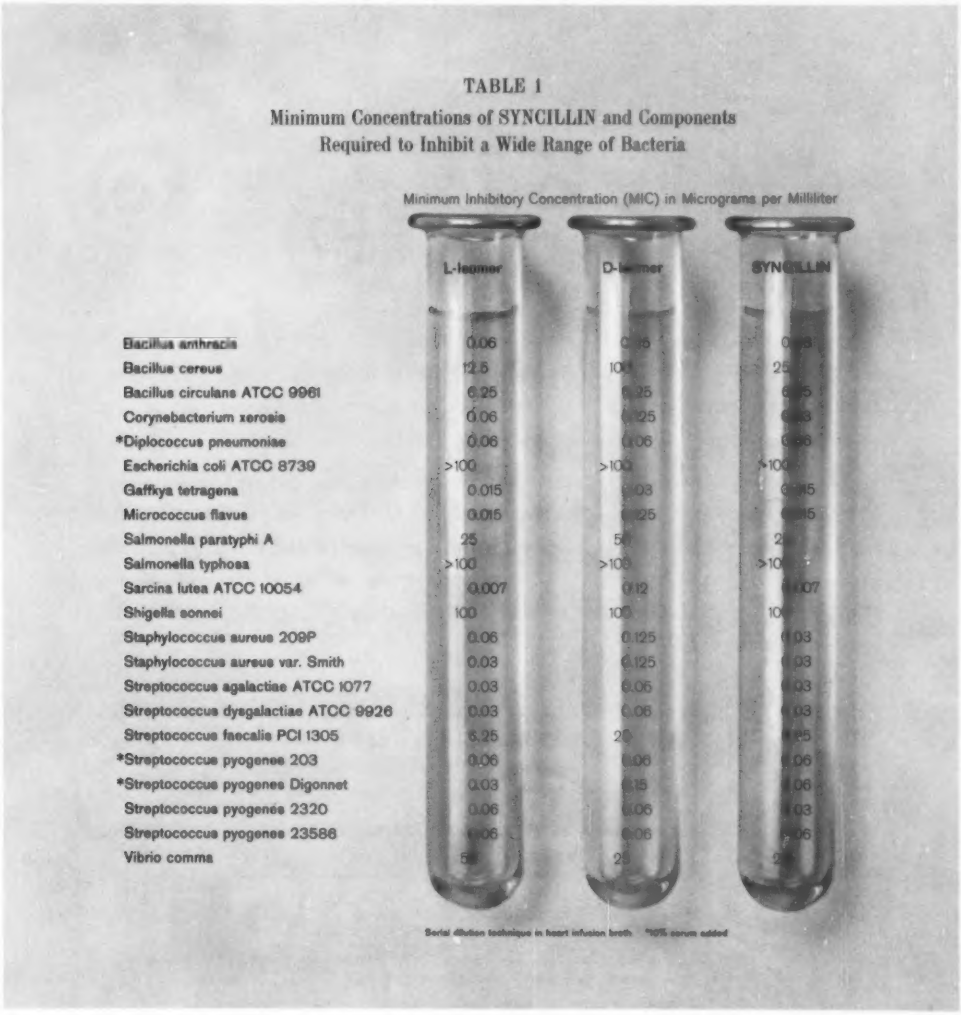
# *ISOMERIC COMPLEMENTARITY DEMONSTRATED IN VITRO*

The *in vitro* minimum inhibitory concentration (MIC) of SYNCILLIN and of each of its two component isomers was determined for a variety of common pathogens and laboratory test organisms. As may be seen from Table 1, all three are highly effective against penicillin-susceptible staphylococci and against pneumococci, streptococci, gonococci, and corynebacteria; all are ineffective against Salmonella, *E. coli*, and other gram-negative coliform bacilli.

SYNCILLIN was more active against many of the test strains including some streptococci and staphylococci than either of its components. This demonstrates *in vitro* the phenomenon of isomeric complementarity.

**TABLE 1**

**Minimum Concentrations of SYNCILLIN and Components Required to Inhibit a Wide Range of Bacteria**



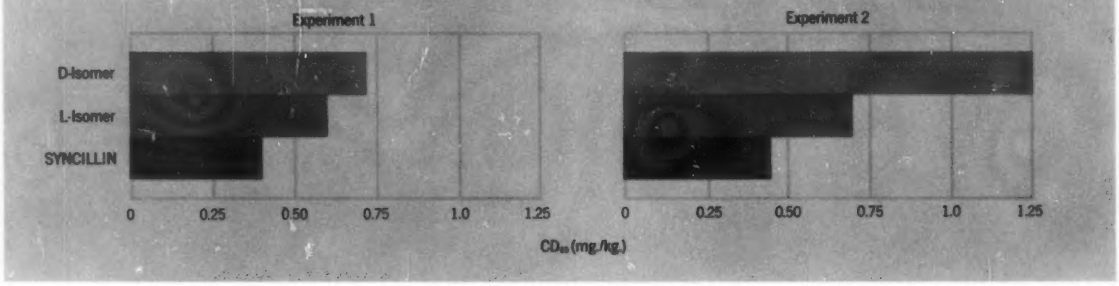

*SYNCILLIN*

*major therapeutic advantages accompany molecular asymmetry*

## *ISOMERIC COMPLEMENTARITY CONFIRMED IN VIVO*

To determine the median curative dose ($CD_{50}$) mice were infected with 100 times the lethal dose of *Staphylococcus aureus*. Each penicillin being tested was administered intramuscularly at the same time, and the dose required to cure half the animals determined. The greater effect of the mixture of the two isomers (SYNCILLIN) is shown in two independent experiments. (See Figure 1.) Note that isomeric complementarity is thus confirmed *in vivo*.

FIGURE 1 — Median Curative Dose ($CD_{50}$) for *Staphylococcus aureus* (var. Smith) Infections

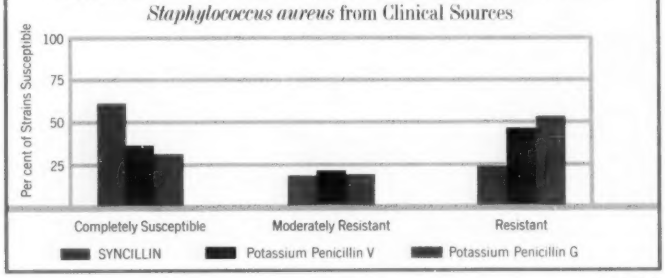



## *MANY STRAINS OF STAPHYLOCOCCI MORE SENSITIVE TO SYNCILLIN*

SYNCILLIN has been tested against a large number of strains of *Staphylococcus aureus* isolated from clinical sources. Many organisms resistant to potassium penicillin G and potassium penicillin V proved sensitive to SYNCILLIN.

Wright[2] performed sensitivity studies on 54 strains, the majority of which were resistant or moderately resistant to penicillin V and penicillin G. Thirty-two (60%) of the strains were sensitive to SYNCILLIN, approximately twice as many as with the other penicillins. (See Figure 2.) In two-thirds of the isolates, SYNCILLIN produced inhibition at concentrations lower than those required for either of the other antibiotics. One strain was more sensitive to penicillin G.

FIGURE 2 – *In Vitro* Sensitivity of 54 Strains of Coagulase-Positive *Staphylococcus aureus* from Clinical Sources




Adapted from Wright[2]

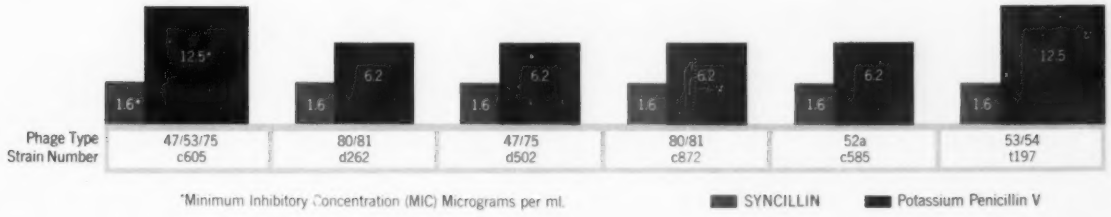
## *SYNCILLIN*

*major therapeutic advantages accompany molecular asymmetry*

Of equal interest are the findings of White.[3] Six penicillin-resistant strains of staphylococci were isolated from hospital infections. None was sensitive to potassium penicillin V. All were sensitive to SYNCILLIN. (See Figure 3.)

FIGURE 3

Minimum Concentrations of SYNCILLIN Required to Inhibit
Hospital Strains of *Staphylococcus aureus* Resistant to Potassium Penicillin V

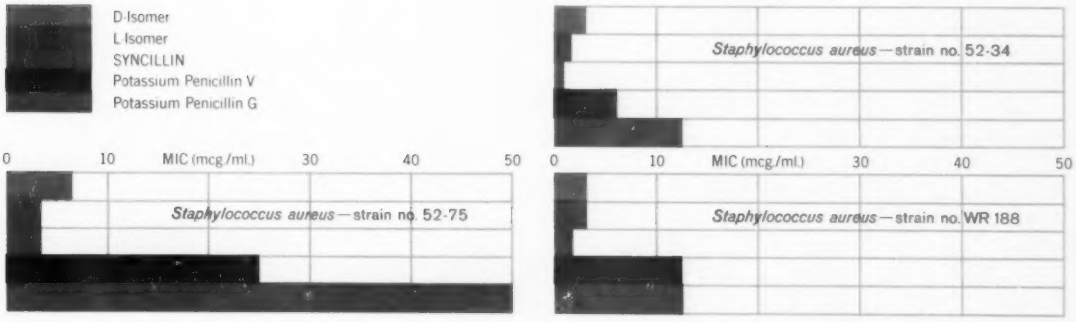



The efficacy of SYNCILLIN against the type 80/81 Staphylococcus (dangerous and widespread in hospitals) is worthy of special attention.

The complementary action of the component isomers is also seen with strains of staphylococci resistant to penicillins. Note that SYNCILLIN is more effective than either isomer against strains 52-34 and WR 188. (See Figure 4.) Against all three strains, SYNCILLIN is effective at concentrations below serum levels, while penicillins V and G are ineffective.

FIGURE 4

Minimum Inhibitory Concentrations (MIC) for Coagulase-Positive
Penicillin-Resistant Strains of *Staphylococcus aureus*




*Isomeric complementarity has thus been demonstrated for:*

— *certain penicillin-susceptible streptococci, staphylococci and corynebacteria* in vitro *(Table 1)*

— *penicillin-susceptible staphylococci* in vivo *(Figure 1)*

— *penicillin-resistant staphylococci* in vitro *(Figure 4)*

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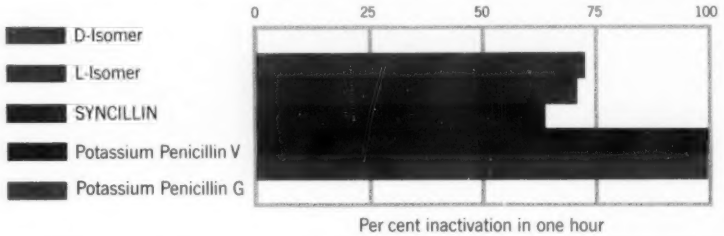
# *ISOMERIC COMPLEMENTARITY SHOWN BY REDUCED RATE OF INACTIVATION BY PENICILLINASE*

Bacterial resistance to penicillin has been attributed to the action of penicillin-inactivating enzymes produced by the invading organisms.[4] As shown in Figure 5, SYNCILLIN is less affected by staphylococcal penicillinase than either of its component isomers – a further demonstration of isomeric complementarity. Further, SYNCILLIN is shown to be less inactivated by this enzyme than penicillin V and penicillin G.

Resistance to SYNCILLIN develops in a slow, step-wise manner characteristic of other penicillins, in contrast to the usually rapid development of resistance to streptomycin.

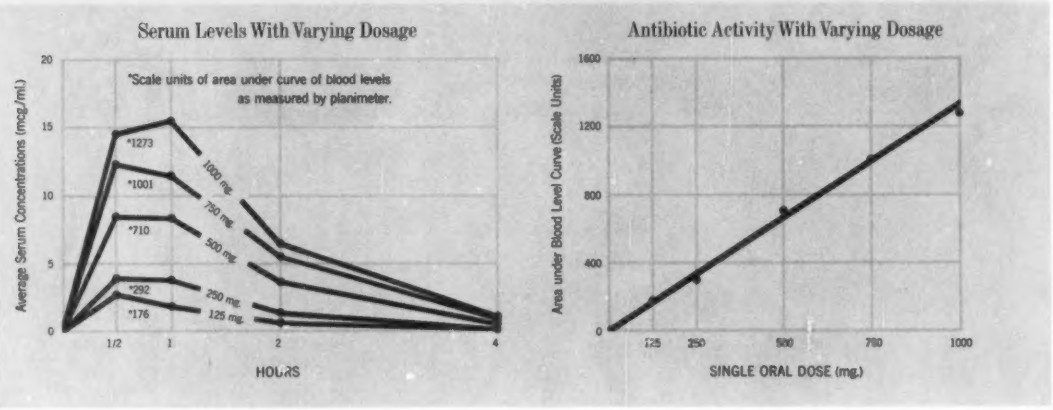
FIGURE 5—Effect of Staphylococcal Penicillinase on Different Penicillins




# *ANTIBIOTIC ACTIVITY DIRECTLY PROPORTIONAL TO ORAL DOSAGE*

Cronk[5] studied blood levels after administering varying amounts of SYNCILLIN. (Figure 6.) Total antibiotic activity (obtained by measuring areas under curves with a planimeter) increases rapidly as the dose is doubled. These data show that increased dosage markedly increases serum concentration and thus may enhance the drug's effectiveness.

FIGURE 6

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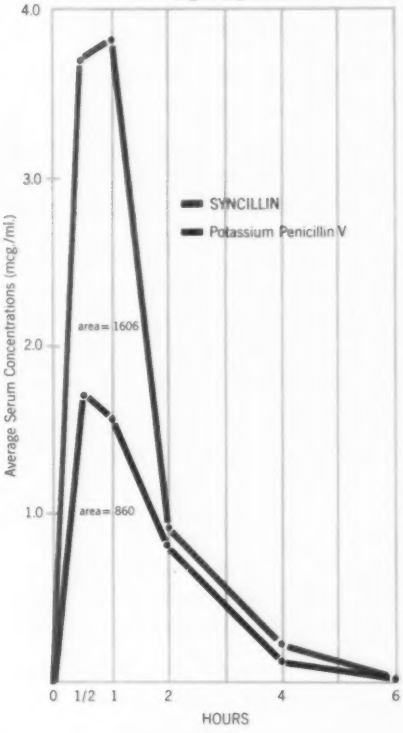
# *BLOOD LEVELS TWICE AS HIGH AS WITH POTASSIUM PENICILLIN V AFTER ORAL ADMINISTRATION*

Wright[6] performed comparative crossover blood level studies on volunteer subjects receiving equivalent amounts of potassium penicillin V and SYNCILLIN. The peak concentrations attained during the first hour after administration were twice as high with SYNCILLIN.

The total antibiotic activity as measured by the area under the curves (see Figure 7) indicates an almost 2 to 1 superiority of SYNCILLIN (1606) over potassium penicillin V (860).

The higher blood levels may be of value with organisms of only moderate penicillin-sensitivity where doubling the blood concentration may be essential for effective bactericidal action. In addition these higher levels may be necessary where there is infection in areas with a poor blood supply.[7] Under these circumstances a higher blood concentration may provide the increased diffusion pressure required to deliver adequate amounts to the tissue.

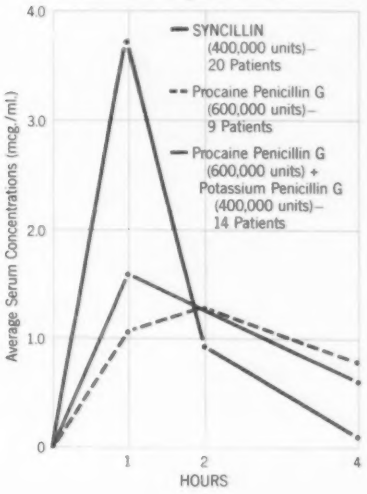
FIGURE 7
20 Subject Crossover
250 mg. Single Dose




# *BLOOD LEVELS MUCH HIGHER THAN WITH INTRAMUSCULAR PENICILLIN G*

In addition, blood levels attained with oral SYNCILLIN[e] are much higher than those with intramuscular penicillin G.[8a, b] (See Figure 8.) Note that the level at one hour for SYNCILLIN (3.8 mcg./ml.) is more than twice as high as with procaine penicillin G, even when reinforced with potassium penicillin G (1.6 mcg./ml.). Since penicillins are *bactericidal,* these intermittent high serum levels can be clinically significant. Thus, SYNCILLIN offers the promise of superior efficacy via the safer oral route.

FIGURE 8—Serum Levels after Oral Administration of SYNCILLIN (250 mg.) and after Intramuscular Injection of Penicillin G

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## *REDUCED HAZARD OF SERIOUS ALLERGENICITY BY SAFER ORAL ROUTE*

SYNCILLIN has been administered in multiple doses to 437 patients and volunteers. One patient developed itching during therapy, possibly an allergic side effect. Another had a purpuric rash, but no relationship to SYNCILLIN was established. No reactions were observed in 9 patients with a known history of sensitivity to penicillin.

While the above data suggests the possibility of reduced allergenic hazard, no definite conclusions may be drawn at this time. *The usual precautions for oral penicillin therapy should be observed.* Patients with histories of asthma, hay fever, urticaria, or previous penicillin-sensitivity should especially be watched carefully. Since SYNCILLIN is administered orally, it may be expected to be safer than parenteral penicillin.

As Flippin[9] recently stated, "... it is well established that serious allergy to the drug [penicillin] is most likely to occur following parenteral administration, especially after repeated intramuscular injections; the oral route is least likely to initiate severe hypersensitivity reactions. This can be explained partly by the fact that when reactions develop following oral medication, they are usually slow enough to treat symptomatically; thus the progression of the reaction can usually be interrupted. . . . In view of the relatively high incidence of severe allergy to injectable penicillin, it would seem advisable to employ oral penicillin routinely, except in the control of infections involving the blood stream, endocardium, meninges, etc., in which cases the parenteral route remains the preferred treatment."

SYNCILLIN, like other penicillins, is essentially free of other toxicity. No hematopoietic, hepatic, or renal toxicity was observed in 210 volunteers receiving 1 gm. daily for 2 to 3 weeks.[10]

## *CLINICAL EFFICACY DEMONSTRATED IN PENICILLIN-SENSITIVE INFECTIONS*

Clinical trials conducted by Blau and Kanof,[11] White,[12] Prigot,[13] Robinson,[14] Dube,[15] Ferguson,[16] Rutenburg,[17] Richardson,[18] Bunn,[19] Cronk,[5] Kligman,[10] and Yow [20] demonstrated the efficacy of SYNCILLIN in a variety of streptococcal, staphylococcal, pneumococcal, and gonococcal infections. Conditions treated included respiratory, skin, soft tissue, wound, and chronic urinary tract infections; acute gonorrhea; cellulitis; septicemia; otitis media; gingivitis; and Vincent's angina. In a few patients SYNCILLIN was used for rheumatic fever or gonorrheal prophylaxis.

One hundred seventy-two of one hundred ninety-six patients responded favorably to SYNCILLIN. The failures included 1 patient with pustular dermatoses, 10 elderly patients with chronic urinary tract infections, 1 patient with gonorrhea, 1 patient with a gram-negative infection, and 10 patients with staphylococcal infections. Lack of response of staphylococcal infections was attributed to the presence of resistant organisms or local suppurative foci requiring drainage.

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Relatively few side effects were encountered. One patient experienced moderate itching of the skin which was controlled by an antihistamine. Another reported pruritus ani which did not interfere with therapy. Diarrhea occurred in 4 instances. There was one purpuric rash, but no relationship to SYNCILLIN could be established.

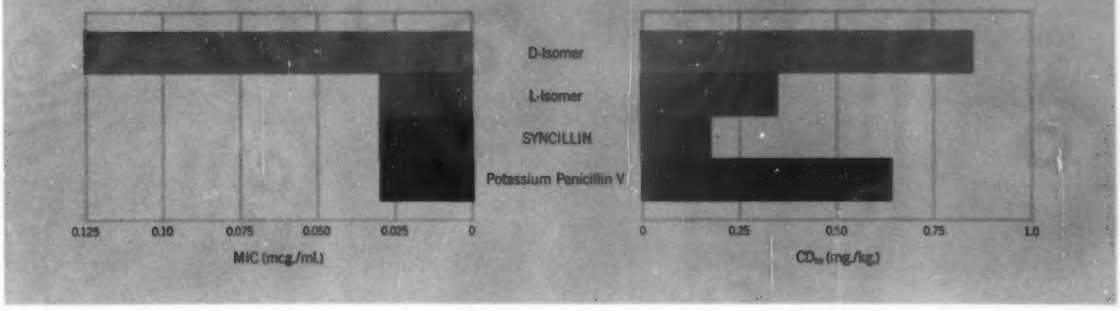
Clinical response usually begins within 24 hours in infections susceptible to SYNCILLIN. Recovery occurs in 4 to 7 days depending upon the severity of the infection. Gonorrheal infections respond very promptly to SYNCILLIN; 500 mg. b.i.d. for two days usually produce bacteriologic cures.

## *IMPROVED ANTIBIOTIC EFFECT FROM COMPLEMENTARY ACTION OF ISOMERS*

SYNCILLIN is a mixture of isomers. The L-isomer is 2 to 17 times more active than the D-isomer against many of the organisms tested. Furthermore, the D- and L-isomers have other distinguishing chemical, pharmacological, and microbiological properties. Their *in vivo* and *in vitro* activities differ for many important pathogens. *Against many of the organisms tested, the combination of isomers* (SYNCILLIN) *is much more active than the stronger isomer alone.* This phenomenon of isomeric complementarity is not always demonstrable, for in a few instances SYNCILLIN is slightly less active.

Isomeric complementarity has previously been demonstrated *in vitro* (Figure 4) and *in vivo* (Figure 1). Figure 9 reveals a third form of superiority related to isomeric complementarity. Equal concentrations of SYNCILLIN and penicillin V were required to inhibit this growth of staphylococci *in vitro*. But, *in vivo*, a much smaller amount of SYNCILLIN *(one-third that of penicillin V)* was effective in an experimental infection with the same strain. These observations on complementary action indicated the advantage of producing the mixture of isomers as the medication to be made available for clinical therapy.

FIGURE 9 — Comparison of $CD_m$ and MIC Values Against *Staphylococcus aureus* (var. Smith)




*Isomeric complementarity has thus been demonstrated for:*

— *certain penicillin-susceptible streptococci, staphylococci and corynebacteria* in vitro *(Table 1)*

— *penicillin-susceptible staphylococci* in vivo *(Figures 1 and 9)*

— *penicillin-resistant staphylococci* in vitro *(Figure 4)*

— *staphylococcal penicillinase antibiotic inactivation (Figure 5)*

*Indications:*

SYNCILLIN is recommended in the treatment of infections caused by pneumococci, streptococci, gonococci, corynebacteria, and penicillin-sensitive staphylococci. In addition, SYNCILLIN is effective against certain strains of staphylococci resistant to other penicillins.

SYNCILLIN, like other oral penicillins, is not recommended at the present time in deep-seated or chronic infections, subacute bacterial endocarditis, meningitis, or syphilis.

*Dosage:*

125 mg. or 250 mg. three times daily, depending on the severity of infection. Larger doses (e.g., 500 mg. t.i.d.) may be used for more severe infections. SYNCILLIN may be administered without regard to meals.

Beta hemolytic streptococcal infections should be treated with SYNCILLIN for at least ten days.

*Precautions:*

While present data suggest the possibility of reduced allergenic hazard, no definite conclusions may be drawn at this time. *Therefore the usual precautions with oral penicillin therapy must be observed.* Patients with histories of asthma, hay fever, urticaria, or previous reactions to penicillin should be watched with special care.

Diarrhea has been reported occasionally following heavy dosage. If this occurs, the interval between dosages should be lengthened.

If superinfection occurs during therapy, appropriate measures should be taken.

Since some strains of staphylococci are resistant to SYNCILLIN as well as to other penicillins, cultures and sensitivity tests should be performed where indicated by clinical judgment. As is true with all antibiotics, clinical response does not always correlate with laboratory bacterial sensitivity reports.

*Supply:*

125 and 250 mg. tablets, bottles of 25 and 100. 125 mg. powder for oral solution, 60 ml. vials.

*References:* 1. Lein, J.: Microbiology report to Bristol Laboratories Inc. 2. Wright, W. W.: Microbiology report to Bristol Laboratories Inc. 3. White, A. C.: Microbiology report to Bristol Laboratories Inc. 4. Dubos, R. J.: Bacterial and Mycotic Infections of Man, 3rd edition, Philadelphia, J. B. Lippincott Co., p. 690. 5. Cronk, G. A.: Clinical report to Bristol Laboratories Inc. 6. Wright, W. W.: Clinical report to Bristol Laboratories Inc. 7. Kass, E. H.: Am. J. Med. *18*:764 (May) 1955. 8a. White, A. C.; Couch, R. A.; Foster, F.; Calloway, J.; Hunter, W., and Knight, V.: in Welch, H. and Marti-Ibañez, F.: Antibiotics Annual — 1955-1956, Medical Encyclopedia, Inc., New York, 1956, p. 490. b. Data on file — at Bristol Laboratories. 9. Flippin, H. F.: Pennsylvania M. J. *62*:864 (June) 1959. 10. Kligman, A.: Clinical report to Bristol Laboratories Inc. 11. Blau, S., and Kanof, N.: Clinical report to Bristol Laboratories Inc. 12. White, A. C.: Clinical report to Bristol Laboratories Inc. 13. Prigot, A.: Clinical report to Bristol Laboratories Inc. 14. Robinson, C.: Clinical report to Bristol Laboratories Inc. 15. Dube, A. H.: Clinical report to Bristol Laboratories Inc. 16. Ferguson, B.: Clinical report to Bristol Laboratories Inc. 17. Rutenburg, A. M.: Clinical report to Bristol Laboratories Inc. 18. Richardson, J. H.: Clinical report to Bristol Laboratories Inc. 19. Bunn, P. A.: Clinical report to Bristol Laboratories Inc. 20. Yow, E. M.: Clinical report to Bristol Laboratories Inc.

BRISTOL

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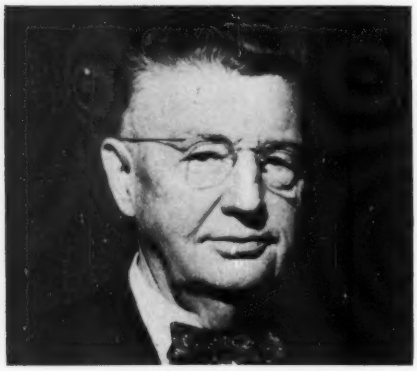
# SYNCILLIN

NEW DECADE,
NEW CHALLENGES

# President's Page



Milton A. Darling

*President*
*Michigan State Medical Society*

To each member of the Michigan State Medical Society, our heartiest greetings and best wishes for good health and happiness throughout this New Year!

Another decade is behind us and we may well pause to take inventory of some of its problems, as well as its accomplishments.

Through our ever-widening community activities we have established a closer liaison in matters of public health, accident prevention, polio, cancer and diabetes control—all factors in improved public relations. New techniques in the field of cardiac surgery have brought acclaim to doctors in our state.

In the difficult field of medico-economics we have made material contribution, but eternal vigilance is necessary.

We have discovered that by extending life expectancy to an astonishing degree, we must assume leadership in helping solve the consequences. Our elder citizens need and deserve our unfailing support and cooperation.

Increasing emphasis has been put on the necessity for graduate medical education with convenient locations for further study arranged geographically. Michigan health conferences are proving of great value, also.

Without any crystal gazing, we willingly accept the challenges of this new decade.

# 1960 Michigan Clinical Institute to Stress Practical Applications

Speakers at the 1960 Michigan Clinical Institute will give special emphasis to the practical application of new medical advances, reports General Chairman R. J. Hubbell, M.D., Suttons Bay.

The total program, he said, was planned to help the practicing physician in his daily work.

The refresher course will begin Tuesday noon and end Friday noon, March 8-11, at the Sheraton-Cadillac Hotel in Detroit.

The opening session on Tuesday afternoon will feature scientific papers on cancer. Wednesday will be General Practice Day with a special afternoon program devoted to trauma. Juvenile delinquency will be discussed by a panel of eminent men on Wednesday evening. Thursday morning will feature speakers on heart and rheumatic fever. The latest developments in the field of internal medicine will be covered in the afternoon. Friday morning speakers will report new advances in obstetrics and gynecology.

For the convenience of MSMS members who will be attending the MCI refresher course, the Committee on Arrangements has placed the registration desk on the fourth floor with the technical exhibits and scientific assembly.

## Operating Room Nurses Institute

The Operating Room Nurses Conference Group of the Michigan State Nurses Association will sponsor a two-day institute on March 10 to 11, 1960, to coincide with the Michigan Clinical Institute.

Some of the subjects to be included in the institute are:

"Operating Room Nursing in Disaster" (with a first-hand report of the activities which took place in the operating room of Hurley Hospital, Flint, during the tornado in that city).

"Psychological Aspects of Operating Room Nursing"

"Care of Cystoscopes and Bronchoscopes"

"Management of Problems in Cardiac Arrest"

"Basic Principles of an Orientation Program"

The nurses planning this program wish to emphasize that all registered professional nurses are cordially invited to attend.

Further information will be published in the *Michigan Nurse*, official publication of the Michigan State Nurses Association, and will be sent to all hospitals in Michigan.

## Other Meetings During MCI

*Michigan Diabetes Association*
Thursday, March 10, 4:00 p.m., Dinner meeting

*Michigan Society of Clinical Hypnosis*
Wednesday, March 9, 6:00 p.m., Dinner meeting

*Michigan Heart Association*
Friday, March 11, 3:30 p.m. meeting

*Michigan Chapter American Academy of Pediatrics*
Tuesday, March 8, Morning and afternoon sessions—Children's Hospital
7:00 p.m., Dinner and speaker—Sheraton-Cadillac

*Michigan Epilepsy Center and Association*
Thursday, March 10. 5:30 p.m., Dinner meeting

*Michigan Proctologic Society*
Thursday, March 10, 6:00 p.m., Dinner meeting

*Operating Room Nurses Institute*
Thursday and Friday, March 10 and 11

*Alumni Association*
*Wayne State University Medical School Alumni Association*
March 8-11, Hospitality Suite

## MSMS Schedules Seminar For County Society Leaders

The Annual MSMS County Secretaries-Public Relations Seminar will be held in Detroit on Saturday and Sunday, January 30 and 31, 1960 at the Sheraton-Cadillac Hotel.

Participants at this seminar will include county medical society presidents, presidents-elect, secretaries, editors, public relations committee chairmen and executive secretaries, plus members of The Council of the State Society.

Here are some of the highlights:

The Saturday afternoon session will cover "The Problems of the Aging and the Challenge of Forand Legislation." National and local speakers will discuss the role medicine must play to make certain that government-dominated medicine is to be averted.

The Saturday night dinner will be sponsored by MSMS to honor Michigan doctors who are presidents of national medical or health associations. This is a new feature of the Seminar, moved up from the Michigan Clinical Institute.

Sunday morning will feature a discussion on the federal tax aspects of medical society activities and a panel on medical society administration and services.

Editors of county medical society bulletins will meet Saturday for a special Editors' Workshop designed to aid in improving all component societies' publications.

## Attorney Urges Medical Examiners

An address advocating medical examiners as opposed to coroners was delivered at the Kalamazoo Academy of Medicine meeting by Jacob A. Dalm, Jr., Kalamazoo County prosecuting attorney.

"What is needed is a pathologist who has medico-legal training and experience," Dalm told the 150 local academy members who attended the monthly dinner meeting at the Hotel Harris.

Dalm, who emphasized he was not criticizing the Kalamazoo County coroner system because the local coroners are doctors, termed the basic failing of the coroner and his jury the "inability to cope with the medical problems their tasks involve."

In discussing the current status of the medical examiner, he pointed out that nineteen of eighty-three Michigan counties, containing 65 per cent of the total state population, have adopted the newer system in this area. Of the sixty-four without medical examiners, fifty-seven have coroners who are laymen.

A recommendation by the Kalamazoo Academy was delayed to permit consideration by the membership.

## RVS Hearings Soon

The next step in the Michigan Relative Value Study project will be a series of hearings with representatives of the various specialty groups.

The Michigan relative value scale questionnaire was mailed to every member of MSMS in November. The dollar charges reported by the doctors were fed into tabulating machines and converted into value units. These value units show relationships between the various professional services.

The MSMS Relative Value Study Committee now will invite the representatives of the special groups to attend conferences to discuss the tabulated information.

MSMS currently is using a modified relative value scale as established by the California Medical Association. At the time of the adoption, it was decided that MSMS should develop its own scale through an independent study in order to accurately and fairly reflect medical practices in Michigan.

Clarence Cook Little, Sc.D., *(right)*, beams with pleasure as he receives the annual citation presented to the Andrew P. Biddle lecturer. G. B. Saltonstall, M.D., did the honors following Dr. Little's address at the MSMS annual session.

# HIGHLIGHTS of MSMS Council Meeting

Seventeen members of The Council attended an all-day meeting November 18, 1959 in the David Whitney House (Wayne County Medical Society headquarters) Detroit, and considered eighty-three items, chief in importance being:

- Financing of the new MSMS building: Treasurer Hyland reviewed progress to date in arranging financing of the new building, advising that a line of credit had been established with a Michigan banking institution at a favorable rate of interest for three years with extension privileges, the money now available as a loan without mortgaging the property. The treasurer was complimented for his arrangement of this transaction.

  For protective purposes, a seventy foot strip of land next to the MSMS building was authorized to be purchased as well as a small parcel of farm land adjoining the northwest corner of the new site, to complete the quadrangle.

  K. H. Johnson, M.D., Lansing, the local representative of the Big Look Committee, was authorized to consult with the realtor re-establishing a new listing price for the MSMS property at 606 Townsend.

  Report on furnishings for the new building was presented by a representative of Architect Minoru Yamasaki & Associates. The matter was referred to the Big Look Committee and the Finance Committee with power to act.
- Medicare: L. Gordon Goodrich, Executive Vice President of Michigan Medical Service, reported that, although Medicare payments were less this year than in previous years, services would be restored by January 1960 which would increase private practice under this program.
- Editor Wilfrid Haughey displayed an aluminated scroll awarded to THE JOURNAL of the Michigan State Medical Society for having the best covers of any state medical society journal; the award was made at the State Medical Journal Advertising Bureau Conference, Chicago, October 27.
- President Milton A. Darling, M.D., Detroit, reported on his attendance at the AMA Regional Conference on Aging, Cleveland, October 28.
- A letter from the Wayne County Medical Society regarding a ruling of the Michigan Department of Social Welfare which precludes social welfare funds to agencies that receive money for care of recipients of public assistance, was thoroughly discussed. The Council supported the Visiting Nurse Association and the Wayne County Medical Society's stand in this matter on the basis that home care is much more economical than hospitalization.

  Appointments:
- The name of A. H. Hirschfeld, M.D., Detroit, was nominated to Governor G. Mennen Williams to serve on the Citizens' Advisory Committee on White House Conference on Aging; Ralph L. Fitts, M.D., Grand Rapids, and Harold W. Woughter, M.D., Flint, were appointed to Geriatrics Committee; Sherwood B. Winslow, M.D., Battle Creek, was nominated to the Medical Advisory Committee of Michigan Hospital Service (to fill the unexpired term of the late Ralph W. Shook, M.D.). O. B. McGillicuddy, M.D., Lansing, was made a member of the Michigan Clinical Institute Press Committee.
- Legal Counsel Lester P. Dodd, presented five legal opinions; a report on a minor survey discrepancy covering the new MSMS property, corrected by quit-claim deeds; and a proposed amendment to MSMS Bylaws, Chapter 10, Section 1 (which was referred to the House of Delegates Committee on Constitution and Bylaws), covering time of election of Council officers.
- The Committees of The Council, including the three standing committees, were, as appointed by A. E. Schiller, M.D., Detroit, confirmed by The Council.
- The Council, upon the recommendation of the Wayne County Medical Society, urged the Michigan Association of the Professions to testify at the forthcoming McNamara Hearings on the Aged, to be held in Detroit, December 10 and 11.
- Public Relations Counsel H. W. Brennamen reported on MSMS exhibits at the state and county fairs with recommendations for 1960; on the McNamara Hearing in Grand Rapids; on the family doctor TV presentation in Kalamazoo and in Grand Rapids; on plans for the annual upper peninsula tour of MSMS Officers; on the MSMS representative to organizational meeting of Michigan State Chamber of Commerce; on the four Michigan regional health conferences; on the new handbook for councilor district medical care insurance committees; and on MAP's "Congress of the Professions" to be held in Detroit, January 22-23.
- A. E. Heustis, M.D., Lansing, Michigan, Health Commissioner, reported on several matters of mutual interest to his Department and to the Michigan State Medical Society.

- The monthly financial reports and bills payable were presented, considered, and approved.
- Committee Reports.—The following were presented: Councilor District Medical Care Insurance Committees of the Twelfth and Thirteenth Districts, meeting of September 3; and of the Second District, October 28; Big Look Committee, October 18; National Defense Committee, October 21; Committee on Arrangements for the 1960 Michigan Clinical Institute, October 22; Maternal Health Committee, October 29; Mental Health Committee, November 5; Advisory Committee of Past Presidents, September 30; Awards Committee, November 18. The minutes of the Permanent Conference Committee (not a committee of MSMS) meeting of October 28 were received.

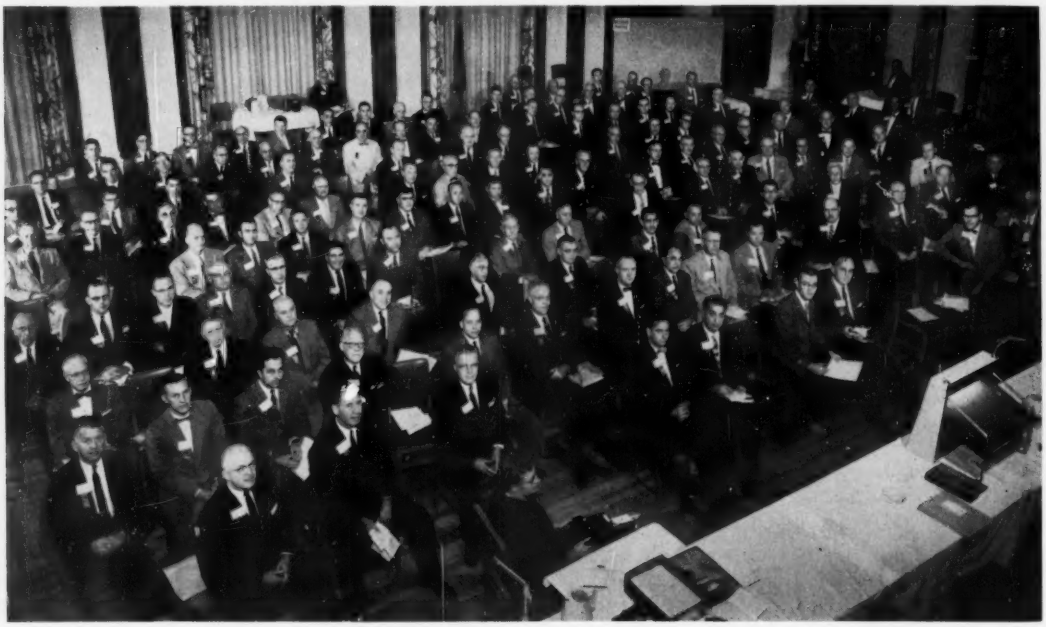
## Re-registration Fee Due

Michigan physicians who have not mailed their "re-registration form" to the Michigan State Board of Registration are urged to do so at once. The forms were mailed to each physician, January 11. If you need a form, please write the Michigan State Board of Registration in Medicine, Stevens T. Mason Building, Lansing.

The Michigan State Board of Registration in Medicine has announced that because the re-registration forms were mailed out late, "the Board has waived the penalty fee of $5.00 on this initial re-registration provided the fee is received prior to March 1, 1960."

## Schedule of Meetings of MSMS Council for 1960

| | |
|---|---|
| Thursday, Friday, Saturday, January 28-29-30 | Sheraton-Cadillac Hotel, Detroit |
| Monday, March 7 | Sheraton-Cadillac Hotel, Detroit (before Michigan Clinical Institute) |
| Wednesday, April 13 | Peninsular Club, Grand Rapids |
| Wednesday, May 18 | Detroit Golf Club, Detroit |
| Wednesday, June 22 | New MSMS building, East Lansing |
| Thursday and Friday, July 14-15 | Grand Hotel, Mackinac Island |
| Wednesday, August 24 | New MSMS building, East Lansing |
| Saturday and Sunday, September 24-25 and Thursday, September 29 | New MSMS headquarters (Dedication on Sunday, September 25); Sheraton-Cadillac Hotel, Detroit |
| Wednesday, November 16 | New MSMS headquarters |
| Wednesday, December 14 | Great Lakes Club, Detroit |



For the first time, there was 100 per cent attendance at the opening session of the 1959 House of Delegates. The three officers are *(front row, left to right)*: D. Bruce Wiley, M.D., secretary; Kenneth H. Johnson, M.D., speaker, and J. J. Lightbody, M.D., vice speaker.


extra
active
REAFFIRMED
AT THE 1959
ANTIBIOTIC SYMPOSIUM
WASHINGTON,
D. C.
Lederle introduces a masterpiece of antibiotic design
10

# Strikingly enhances the traditional advantages of broad-spectrum antibiotics...

## for greater patient-physician benefit

DECLOMYCIN is a unique fermentation product of a strain of *Streptomyces aureofaciens*—the parent organism of AUREOMYCIN®* and ACHROMYCIN.®†

DECLOMYCIN singularly achieves:

- far greater antibiotic activity with far less drug[1,4-6,8,13,14]
- greater stability in body media[4-6,8]
- unrelenting peak activity throughout therapy[4,5]
- "extra-day" protection through sustained activity[1,4]

DECLOMYCIN retains:

- unsurpassed broad-spectrum range of activity[4,6,10-12,14]
- rapid activity[1,4,5,8,13]
- excellent toleration[1-7,9,11,12]
- effectiveness against infection[2-5,7,9,11,12]
- rapid diffusion in body tissues and fluids [1,4,5,8]

*Chlortetracycline Lederle †Tetracycline Lederle

# DECLO

Demethylchlortetracycline Lederle

# Far greater antibiotic activity with far less antibiotic

REAFFIRMED AT THE 1959 ANTIBIOTIC SYMPOSIUM WASHINGTON, D. C.

Milligram for milligram, DECLOMYCIN brand of Demethylchlortetracycline has two to four times the inhibitory capacity of tetracycline against susceptible organisms. Thus, DECLOMYCIN has the advantage of providing significantly higher serum *activity* levels with significantly reduced drug intake.*

Actually, DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of milligram intake of drug reduces hazards of related physical effect on intestinal mucosa.

*Activity level is a far more meaningful basis of comparison than quantitative blood levels, as Hirsch and Finland note. Action upon pathogens is the ultimate value.
(Hirsch, H. A. and Finland, M.: Antibacterial Activity of Serum of Normal Subjects after Oral Doses of Demethylchlortetracycline, Chlortetracycline and Oxytetracycline. *New England J. Med.* 260:1099 (May 28) 1959.)

MYCIN

# Unrelenting peak antimicrobial attack throughout therapy

The high level of DECLOMYCIN activity is uniquely sustained. It is not just an initial phenomenon but is constant—maintained on each day of treatment and between doses—without noticeable diminution of intensity. Peak-and-valley control is eliminated, favoring continuous suppression of pathogens and consequent improvement.

This DECLOMYCIN constant is achieved through remarkably greater stability in body fluids, resistance to degradation and a low rate of renal clearance—all supporting antibiotic activity for extended periods.


# DECLO

Demethylchlortetracycline Lederle

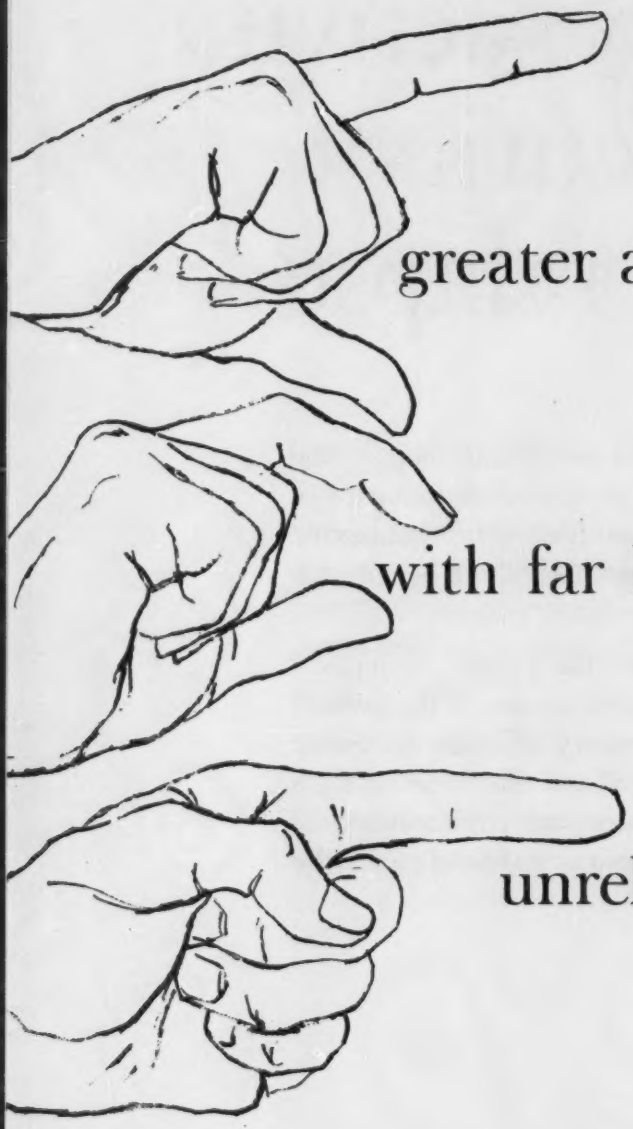
# "Extra-day" activity for security against relapse

DECLOMYCIN maintains significant antibacterial activity for one to two days after discontinuance of dosage—a major distinction from other antibiotics. Previous drugs have declined abruptly in activity following withdrawal.

DECLOMYCIN thus gives the patient an unusual degree of protection against resurgence of the primary infection, and against secondary infection...sequelae not infrequently encountered and often resembling a "resistance problem." Consequently, reinstitution of therapy or a change in therapy should rarely be necessary.

MYCIN

# A masterpiece of



greater antibiotic activity

with far less antibiotic intake

unrelenting peak attack

—enhancing the unsurpassed features of tetracycline . . . for greater physician-patient benefits

# DECLO

Demethylchlortetracycline Lederle

# antibiotic design

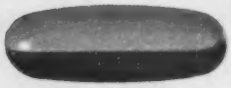
REAFFIRMED
AT THE 1959
ANTIBIOTIC SYMPOSIUM
WASHINGTON,
D. C.

plus
"extra-
day"
activity

FOR PROTECTION
AGAINST
RELAPSE

MYCIN

# A major contribution of Lederle research



in the distinctive dry-filled duotone capsule

# DECLOMYCIN®

Demethylchlortetracycline Lederle

Available as: Capsules, 150 mg.
Pediatric Drops, 60 mg. per cc.
Oral Suspension, 75 mg. per 5 cc. tsp.

**Reports presented at Seventh Annual Symposium on Antibiotics, Mayflower Hotel, Washington, D. C., November 4-6, 1959:** 1. Boger, W. P. and Gavin, J. J.: Demethylchlortetracycline: Serum Concentration Studies and Cerebrospinal Fluid Diffusion. 2. Chávez Max, G.: Therapeutic Evaluation of Demethylchlortetracycline in Human Brucellosis. 3. Duke, C. J.; Katz, S., and Donohoe, R. F.: Demethylchlortetracycline in the Treatment of Pneumonia. 4. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Observations on Demethylchlortetracycline. 5. Fujii, R.; Ichihashi, H.; Minamitani, M.; Konno, M., and Ishibashi, T.: Clinical Results with Demethylchlortetracycline in Pediatrics and Comparative Studies with Other Tetracyclines. 6. Garrod, L. P. and Waterworth, P. M.: The Relative Merits of the Four Tetracyclines. 7. Kanof, N. B. and Blau, S.: A Clinical Evaluation of Declomycin Demethylchlortetracycline in the Treatment of Pustular Dermatoses. 8. Kunin, C. M.; Dornbush, A. C., and Finland, M.: Distribution and Excretion of Four Tetracycline Analogues in Normal Men. 9. Marmell, M. and Prigot, A.: The Use of Demethylchlortetracycline in Gonorrhea, Lymphogranuloma Venereum, and Donovanosis. 10. Olarte, J.: The Sensitivity of Selected Strains of Shigella, Salmonella and Enteropathogenic *Escherichia coli* to Demethylchlortetracycline and Tetracycline. 11. Perry, D. M.; Hall, G. A., and Kirby, W. M. M.: Demethylchlortetracycline: A Clinical and Laboratory Appraisal. 12. Roberts, M. S.; Seneca, H., and Lattimer, J. K.: Demethylchlortetracycline in Genitourinary Infections. 13. Ross, S.; Puig, J. R.; and Zaremba, E. A.: Absorption of Demethylchlortetracycline in Infants and Children: Some Preliminary Observations. 14. Vineyard, J. P.; Hogan, J., and Sanford, J. P.: Clinical and Laboratory Evaluation of Demethylchlortetracycline.

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Declomycin Caps
150 mg.
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*AMA PR INSTITUTE*

# *The Dangers of Governmental Health Service*

By ROLF SCHLOGELL, M.D.

*Cologne, Germany*

*(Because of the importance of this subject, The Council of MSMS directed that excerpts of Doctor Schlogell's remarks be reprinted. The talk, delivered in Chicago, August 20, 1959, has been condensed by R. W. Teed, M.D., chairman of the MSMS Public Relations Committee.)*

Whenever protection against social and economic risks of illness is provided in any way other than the personal savings fund of the protected person, three participants are involved, namely: (a) the protected person who is the potential patient of the doctor, hospital, and so on; (b) the carrier of the protection, and (c) the individual doctor, himself. Hence, in the government health service the participants become: (a) the entire population, or at least a major percentage of it; (b) the government or the administrative governmental authority; and (c) the medical profession.

When you recognize the various aspects and difficulties that arise between the three participants under an insurance system, consider how much more complicated and difficult it will become when the state, itself, becomes the third participant and, in so doing, automatically loses its neutral position as a mediator between the groups or between individuals.

* * *

THE DANGERS OF THE government health service are obvious. Let me begin with the material dangers or arguments, which are more apparent than the idealistic.

In every government health system there is a vast financial danger. By this I do not mean the excessive growth of the cost originating from the government health system—an excellent example being the British National Health Service, in which the budget figure for this year was 650 million pounds ($1,821 billion).

I believe that we have already resigned ourselves, in too great a degree, to our fate by complying with the complicated machinery of today's social life in surrendering our individual freedoms in order to guarantee a frictionless living together as a whole.

* * *

ALREADY MANY OF US HAVE, in this way, lost the ability to judge whether or not the abandonment of rights and freedoms is worth the personal price we pay. If we really believe in the Western ideals of freedom, we should most earnestly consider whether or not the abandonment of personal freedom is really an advantage to the whole public, and whether these advantages are far greater than their inherent dangers. This decision can be reached only after careful consideration.

The dangers that arise from a government health service must be seen, especially when it deprives groups of people (economically and socially capable of making their own decisions as to the type of health protection they desire for themselves and their families) of the freedom to choose and literally forces these people into a governmentally-administered system.

A vast difference exists between the legislation that requires people, who can afford to protect themselves against the risks of illness, to invest their own funds in order to insure themselves, and the legislation that forces these same people into a system administered and financed by the state, itself.

* * *

THE FIRST METHOD provides each person with the right to choose the kind of protection he desires. The second method destroys the freedom of decision.

Ever since institutions for providing protection against the risk of illness and its economic consequences were developed in Central Europe, consideration has been given to whether or not, and to what extent, the preservation of freedom is possible or desirable in these institutions, or if the limitation of freedom is necessary with respect to the so-called higher interests of the public.

Health and illness are among our most individual traits. Health is a changing, surging condition divested of normative measure. Health is not a commercial commodity but a highly complex and complicated state which cannot be collectively evaluated nor regulated. Illness, as the negative aspect of health, must be classified in the same category. It cannot be analyzed in the same manner as a defunct engine. The cure of illness does not lie in a legal claim, nor is health a purchasable right. Health is a gift from God.

Psychology has demonstrated the extent to which illness and health are individual conditions. Hence, if it is true that individual conditions cannot be collectively treated, it is our duty to prevent the dangers inherent in equalization procedures.

* * *

THE DOCTOR-PATIENT RELATIONSHIP has always been one of a very special type. It is a combination of that intimate relationship which exists in marriage, and that of the priest and his parishioner—the most personal relationship known in our world.

In this relationship, the loss of freedom of either individual has a direct effect upon the other individual. It seems to me that the importance of the interdependence of the doctor and patient is not fully appreciated in our civilization.

I am convinced that a government health service restricts four fundamental freedoms to a higher degree than any other insurance systems, whether purely private or based upon legislation. These restrictions are:

1. The freedom of the patient to choose the doctor in whom he has confidence.
2. The freedom of the doctor to refuse further treatment to the patient if the confidence each has in the other—the physiological basis in the healing of illness is destroyed.
3. The freedom of the doctor to practice his profession according to the rules of medical art and science—freedom to select the suitable techniques in diagnosis and therapy, and to reject those that are unnecessary or even detrimental.
4. The freedom of the supervision of the doctor by professionally qualified groups—free from the authoritative influence of laymen.

Finally, I might add another especially important danger in the governmental service. This is the patient's loss in choosing the system of illness protection he desires, and developing his own relationship with it.

* * *

ALL OF THE group of dangers we have mentioned also exist in almost every insurance institution or welfare system. Hence, these dangers are the main issues involved whenever there are disagreements between the medical profession and the social security institutions.

Bearing in mind the difficulties in this topic, the many varieties of insurance and welfare systems, and the types of organizations in government health services, it was obviously impossible for me to deal with this important topic in more detail. I have tried to present some of my personal thoughts and philosophy on this subject, which may have proved that there are many and important dangers in the socio-philosophic or, may I say, socio-romantic ideal and ideas on a governmentally-owned protection for every citizen of a state against the risk of illness.

* * *

IN MY OPINION the most important of these dangers are:

1. The attempt to equalize individuals and standardize various conditions.
2. The possible restriction of freedoms which are the decisive factors in the doctor-patient relationship.
3. The possibility that a necessary development in the field of health policies will be subordinated to the requirements of political economics.

Finally, I am opposed to the state intruding itself into another field of human life as founder, carrier, and administrator—a field which can be covered by other means without the regulation and with more freedom for each individual.


WHENEVER COUGH THERAPY IS INDICATED

# Hycomine®

SYRUP

THE *complete* Rx FOR COUGH CONTROL

*cough sedative / antihistamine / expectorant*

- relieves cough and associated symptoms in 15-20 minutes
- effective for 6 hours or longer
- promotes expectoration
- rarely constipates
- agreeably cherry-flavored

NOW MORE EFFECTIVE THAN EVER WITH THE NASAL DECONGESTANT PHENYLEPHRINE

Each teaspoonful (5 cc.) of HYCOMINE* contains:

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| Hycodan® | | |
| Dihydrocodeinone Bitartrate (Warning: May be habit-forming) | 5 mg. | 6.5 mg. |
| Homatropine Methylbromide | 1.5 mg. | |
| Pyrilamine Maleate | | 12.5 mg. |
| Phenylephrine Hydrochloride | | 10 mg. |
| Ammonium Chloride | | 60 mg. |
| Sodium Citrate | | 85 mg. |

Supplied: As a pleasant-to-take syrup. May be habit-forming. Federal law permits oral prescription.

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*Literature on request*

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* U.S. Pat. 2,630,400

## *Bay Publicizes Speakers Bureau*

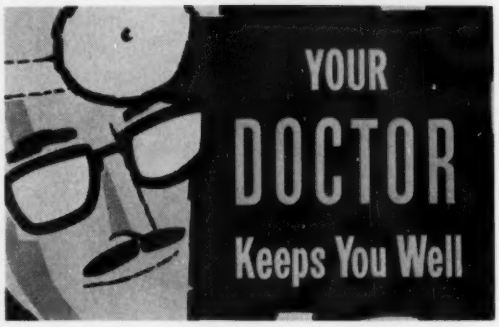
As a public relations measure, the Bay-Arenac-Iosco County Medical Society has established a Medical Speakers Bureau as a service to community organizations and groups.

To announce the formation of the Speakers Bureau, Chairman W. G. Gamble, Jr., M.D., mailed a letter to clubs and organizations in the area, inviting them to make use of the medical society service. The letter followed newspaper publicity.

Doctor Gamble reports that the Bureau succeeded so well during its first year of operation that a second letter of invitation was sent out for 1959-60.

---

Instead of fighting the U.M.W., Pennsylvania physicians have voted to launch a $150,000-per-year public relations program to convince people of the following: "To the extent to which care has been substandard, we wish to elevate it. To the extent that economic abuses have developed, they should be curbed and prevented. To the extent that patients and third parties have been aggrieved, we wish to provide . . . equity and justice."—*Medical Economics*, November 9, 1959.




"Your Doctor Keeps You Well" is the message carried this month on thousands of linen supply delivery trucks across the country. Each month, the Linen Supply Association of America dedicates its poster project to a different cause or group.

---

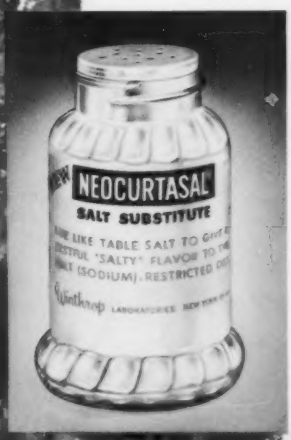
"In modern society, the necessary concentration of production facilities some day will have to be supported by well-informed public opinion.—Raymond Aron, French economist, in early 19th century.

# NO SALT... *but seasoned*

**A meal of even the most colorful and the most meticulously prepared food can be dreary without salt. Neocurtasal, for the patient on a low sodium diet, brings back flavor to food and makes eating a pleasure once more. Neocurtasal is also valuable for preventing potassium deficiency (weakness, etc.) in patients on diuretic therapy with chlorothiazide or its derivatives.**

# Neocurtasal®

*An excellent salt replacement for Salt Free* (LOW SODIUM) *Diets*




*Neocurtasal contains potassium chloride, potassium glutamate, glutamic acid, calcium silicate and potassium iodide (0.01 per cent)*

**Supplied in 2 oz. shakers and 8 oz. bottles.**

*Sold Only through Drugstores*

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ERT GOMMI

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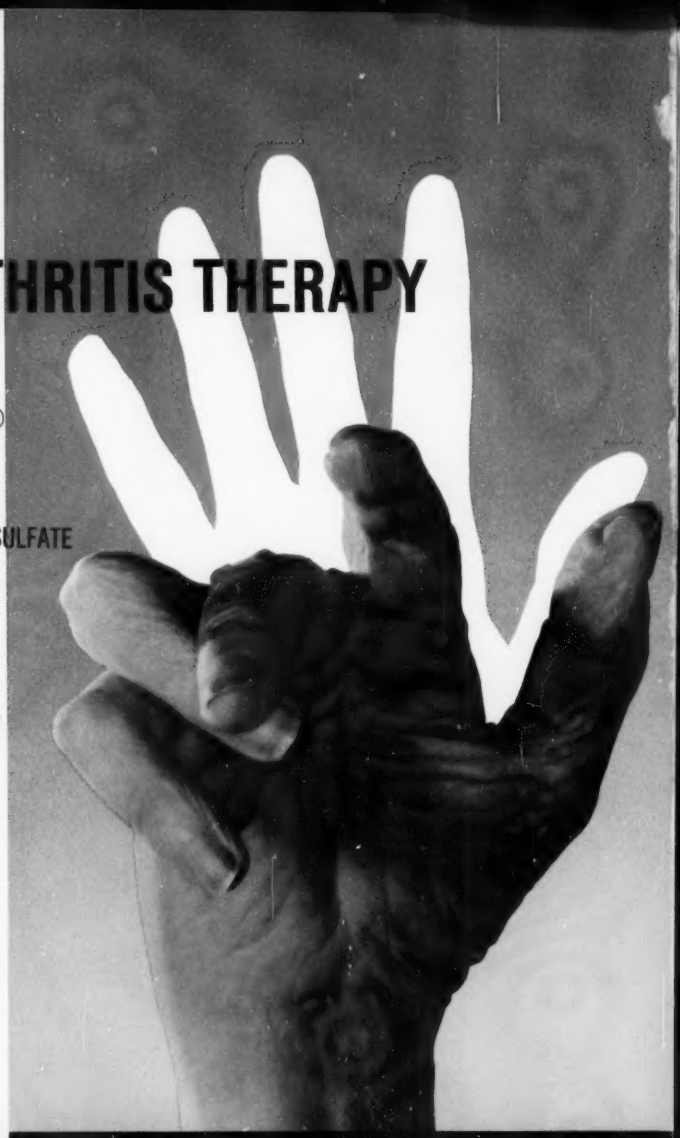
# MAINSTAY

## OF RHEUMATOID ARTHRITIS THERAPY

# Plaquenil® SULFATE

Brand of hydroxychloroquine sulfate



## *New Long Term Chemotherapy of* RHEUMATOID ARTHRITIS

"Whatever else may be needed from time to time in the management of individual cases, these drugs [Plaquenil and Aralen] should always be given a prolonged trial (at least six months) as the 'mainstay' of therapy."

***Bagnall, A. W. (Univ. British Columbia, Vancouver, B.C.): A.M.A. Clinical Meeting (Scientific Section, Exhibit No. 124), Minneapolis, Minnesota, Dec. 2-5, 1958.***

"The 4-aminoquinoline drugs (Plaquenil and Aralen) together with supplemental agents administered in nontoxic doses effectively maintained suppression of the disease in 83 per cent of 194 patients followed for 18 months."

***Scherbel, A. L.; Harrison, J. W., and Atdjian, Martin:*** **Cleveland Clin. Quart. *25:95, April, 1958.***

"When used in tolerated dosage and over a sufficient period of time, there appears to be a tremendous therapeutic potential in the antimalarial drugs. . . . Plaquenil in this study did not have as many side effects as Aralen and thus appears to be a more practical compound."

***Cramer, Quentin (Kansas City):*** **Missouri Med. *55:1203, Nov., 1958.***

Plaquenil is the hydroxy derivative of Aralen® and is available as Plaquenil sulfate in tablets of 200 mg. (bottles of 100).

*Average Dosage:*

*INITIAL*–400 to 600 mg. (1 tablet 2 or 3 times daily)

*MAINTENANCE*–200 to 400 mg. (1 tablet once or twice daily)

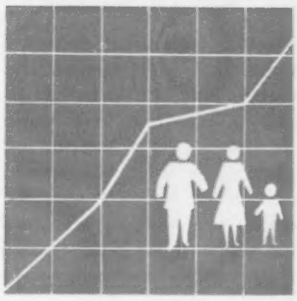
*Write for Plaquenil booklet discussing clinical experience, dosage, tolerance, precautions, etc., in detail.*

Winthrop

Plaquenil (brand of hydroxychloroquine) and Aralen (brand of chloroquine), trademarks reg. U.S. Pat. Off.

# *Facts Used by Forand Bill Backers Are Incomplete, Inconclusive*





Liquid asset holdings of persons over sixty-five have been ignored by groups supporting legislation which would provide government health care for the aged.

The fact that the over-sixty-five age group holds "relatively substantial" liquid assets makes questionable the need for legislation ". . . designed to compel those under sixty-five to pay . . . medical care costs of those over sixty-five, regardless of financial status."

These are conclusions of a study by the American Medical Association's Department of Economic Research on "Financial Assets of the Aged and Forand-Type Legislation."

* * *

THE STUDY POINTED OUT that the Federal Reserve Board's Survey of Consumer Finances shows that between 1949 and 1958, persons over sixty-five accumulated liquid assets faster than any other age group.

Three out of four persons (74 per cent) in this age group owned liquid assets in some form in 1958, according to the FRB survey. Persons over sixty-five had the highest median value in liquid asset holdings—$800 for all aged persons and $2,450 for the 74 per cent holding liquid assets.

Liquid assets include bank savings and checking accounts, postal savings, savings bonds, and shares in savings and loan associations and credit unions. They do not include stocks, other types of bonds, homes, and other real estate.

The AMA study said that while nearly 75 per cent of the aged had incomes of $3,000 or less in 1957, nearly half the persons in that income bracket had liquid assets of $500 or more in 1958.

In addition, eight of every ten persons over sixty-five with income of $3,000 to $5,000 in 1958 held assets of $500 or more and 57 per cent had liquid holdings valued at $2,000 and above.

* * *

THE STUDY said these figures suggest that the problem of the aged is not one of money income and age, nor a group problem.

"There are indeed chronic problems of aging and the aged, but . . . they are individual problems of individual human beings," the report said.

"To the extent it can be argued that some people cannot afford medical care, the argument calls either for an extension of the deductible provisions in income tax laws or, at most, for some subsidization of the poverty-stricken."

The study said proponents of the Forand bill have often quoted a figure that three-fifths of all people over sixty-five had less than $1,000 in money income in 1956 and 1957.

It said this figure pictures the aged as poverty-stricken, but it pointed out that in 1958, 47 per cent of all people between fourteen and sixty-five had $1,000 or less income. But the median family income was approximately $6,000.

* * *

THE STUDY SAID it should be remembered that the money income figure quoted for the aged by Forand-bill backers refers to individual incomes—not family income.

Department members making the study were Arthur Kemp, Ph.D., director; Leonard W. Martin, Ph.D., assistant director; and Miss Cynthia Harkness, research assistant.

## *State C of C Organized*

The formal organization meeting of the new Michigan State Chamber of Commerce was held in Lansing on December 9. The State Chamber, according to its founders, is conceived as a "workshop" to produce new and better ways of utilizing our state's business and industrial resources. To accomplish this worthy objective, the Chamber will seek to co-ordinate civic, professional, industrial, agricultural and recreational activities, will work for better legislation, and will cooperate with local chambers and associations.

## *Contends Instruction Needed in Health Insurance Principles*

Medical schools and medical societies should undertake regular instruction of doctors and students in the use and principles of health insurance, contends Haddon M. Carryer, M.D., Rochester, Minnesota.

Commenting on the "many problems in common" of the medical profession and the health insurance business, he made the suggestion in his address to the recent insurance forum of the Health Insurance Association of America in New York City.

Pointing to the "current efforts on the part of both the medical and insurance profession to extend the usefulness of health insurance," Doctor Carryer reported on major common problems toward achieving this goal, and declared:

"These problems are magnified because we are constantly beset by outside planners who would discard gradual evolutionary processes and take a far more radical tack into plans not best for the people whether they be patients or policyholders."

Among problems listed by Dr. Carryer were the costs of processing large numbers of claims, the "failure by patients to understand the nature of the insurance and of benefits to which they are entitled," and not fully understood features of some of the newest types of policies.

"Another problem concerns the matter of indoctrination of physicians with respect to insurance matters," he told the audience of insurance executives.

"Instruction should be started in the medical schools with a series of lectures.

"It should extend to the county medical society and state medical society levels so that physicians understand clearly the significance of such terms as insurance, comprehensive insurance, catastrophic insurance, corridors, deductibles and coinsurance.

"When an insurance program, especially one involving comprehensive care, is introduced in the community, a review of the insurance principles involved should be an integral part of that introduction.

"The omission of such an indoctrination only leads to misunderstanding, over-utilization and bad public relations—bad both for the insurance company and for the physician who may not thoroughly understand insurance principles."

## *"Medical Care" Up in Consumer Index*

"Medical Care" consumer price index rose slightly to 152.2 in September, according to the monthly report by the Labor Department. For all goods and services combined, the rise was 0.3 per cent, to an index figure of 125.2 (1947-49=100). In New York City, the "Medical Care" index rose 2.4 per cent, which accounted in large measure for the increase nationally.

## *Old Age Survivors, Disability Insurance*

Latest figures from Social Security Administration show that in August 1959, payments to beneficiaries of old age, survivors, and disability insurance were being made at an annual rate of $9,864 million. August payments approximated $822 million. Checks are being mailed monthly to 13,396,000 persons: Nearly eleven million of them aged sixty-two and over; about two million young survivors and dependents, and some 300,000 in the fifty to sixty-four age group who are receiving disability payments.

"There continue to be great advances in building better relations between the health insurance business and the medical and hospital professions," reports J. Grant Irving, M.D., chairman of the Health Insurance Council's Medical Relations Committee. He made this observation at the winter HIC meeting.

Doctor Irving cited growing contact with the American Medical Association through meeting of insurance company presidents and the officers of the AMA. He noted these meetings have been of great value in providing an exchange of ideas and viewpoints.

# C. A. Conshus, M.D., Says . . .


If bleeding persists from the rectum,

Might be piles; have your doctor inspectem.

But it could be malignant,

So don't be indignant

If he looks up your tail to dectectem.

Old times — rectal cancer — no hope.

The patient was eased out with dope.

Now we find them in time,

Before they reach prime,

With our new up-to-date proctoscope.

POINT - Rectum

DANGER SIGNAL - Rectal bleeding or change in bowel habit.

Limericks by Sydney B. Carpender—Drawings by Robert Toombs.
Reprinted from the *Pennsylvania Medical Journal*, November 1957-October 1958. By permission of the Commission on Cancer, The Medical Society of the State of Pennsylvania and the American Cancer Society, Pennsylvania Division, Inc.

# Doctors, too, like "Premarin."

THE doctor's room in the hospital is used for a variety of reasons. Most any morning, you will find the internist talking with the surgeon, the resident discussing a case with the gynecologist, or the pediatrician in for a cigarette. It's sort of a club, this room, and it's a good place to get the low-down on "Premarin" therapy.

If you listen, you'll learn not only that doctors like "Premarin," but *why* they like it.

The reasons are fairly simple. Doctors like "Premarin," in the first place, because it really relieves the symptoms of the menopause. It doesn't just mask them — it replaces what the patient lacks — natural estrogen. Furthermore, if the patient is suffering from headache, insomnia, and arthritic-like symptoms due to estrogen deficiency, "Premarin" takes care of that, too.

"Premarin," conjugated estrogens (equine), is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

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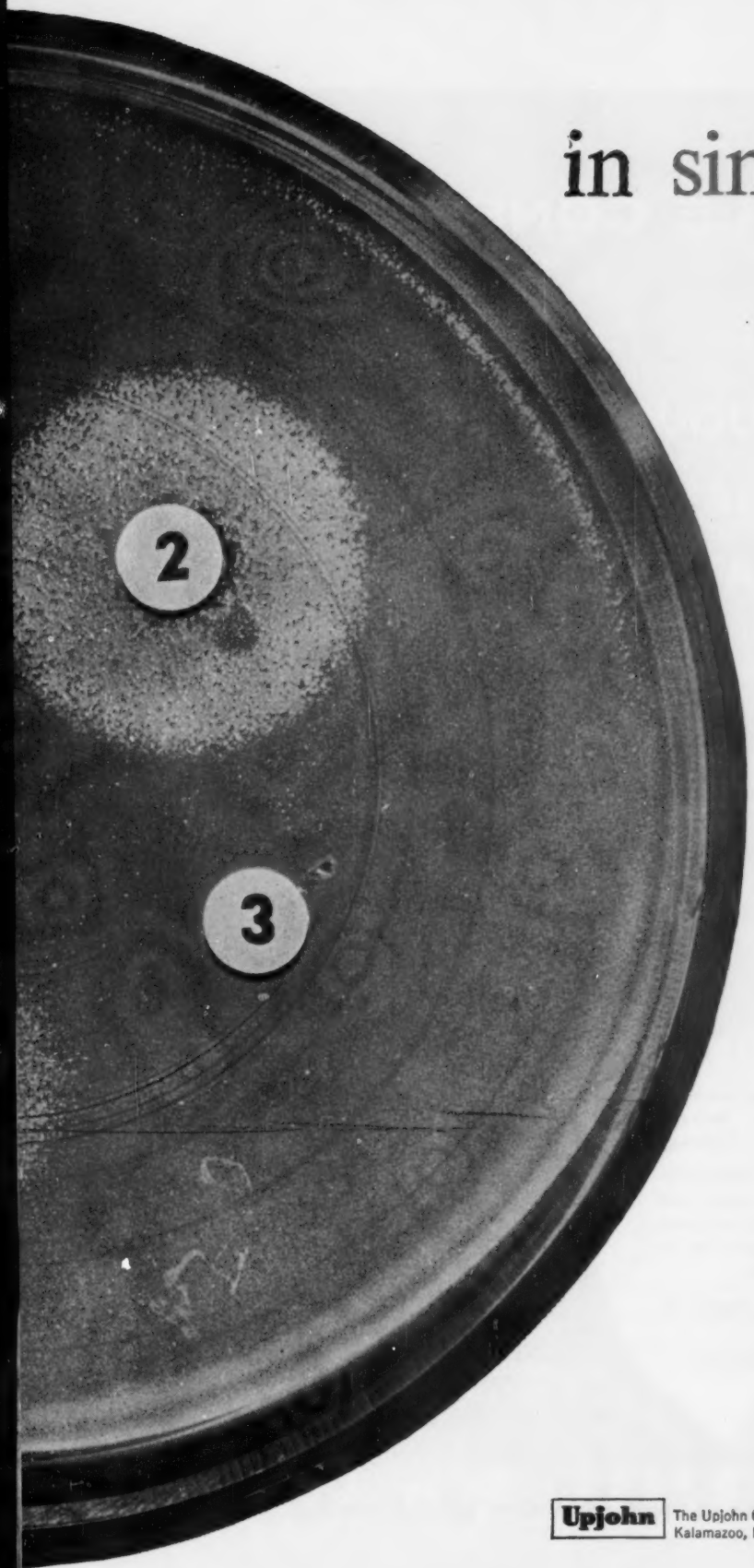
# This is Panalba performance...




# in sinusitis

. . . into a mixed culture of the four organisms commonly involved in sinusitis . . . *Str. hemolyticus, D. pneumoniae, H. influenzae* and *Staph. aureus* (in this case a resistant strain) . . . we introduce the five most frequently used antibiotics.

Twenty-four hours later (in this greatly enlarged photograph), note that only *one* of the five leading antibiotics has stopped *all* the organisms, including the resistant staph! This is Panalba.

In your next patient with sinusitis . . . in *all* your patients with potentially-serious infections . . . provide this extra protection with your prescription:

**Dosage—1 or 2 capsules 3 or 4 times a day.**
**Supplied—Capsules containing Panmycin phosphate equivalent to 250 mg. tetracycline hydrochloride, and 125 mg. Albamycin as novobiocin sodium, in bottles of 16 and 100.**
***Now available:*** **new Panalba Half-Strength Capsules in bottles of 16 and 100.**

# Panalba*

(Panmycin* Phosphate plus Albamycin*)

The broad-spectrum antibiotic of *first* resort

Upjohn The Upjohn Company Kalamazoo, Michigan

*TRADEMARK, REG. U. S. PAT. OFF.


# saturation doses – the hard way!

Each of these food portions contains a saturation dose of one of the water-soluble B vitamins or C. The easy way to provide such quantities of these vitamins with speed, safety and economy is to prescribe Allbee with C. Recommended in pregnancy, deficiency states, digestive dysfunction and convalescence.

| In each Allbee with C: | | As much as:* |
|---|---|---|
| Thiamine mononitrate ($B_1$) | 15 mg. | 6.9 lbs. of fried bacon |
| Riboflavin ($B_2$) | 10 mg. | 31½ ozs. of liverwurst |
| Pyridoxine HCl ($B_6$) | 5 mg. | 2 lbs. of yellow corn |
| Nicotinamide | 50 mg. | 11 ozs. of roasted peanuts |
| Calcium pantothenate | 10 mg. | ¼ lb. of fried beef liver |
| **Ascorbic acid (Vitamin C)** | **250 mg.** | ¾ lb. of cooked broccoli |

*These common foods are among the richest sources of B vitamins and ascorbic acid. H. A. Wooster, Jr., Nutritional Data, 2nd Ed., Pittsburgh, 1954.

# Allbee® with C

Robins

A. H. ROBINS COMPANY, INC.
RICHMOND 20, VIRGINIA

*the beauty of these antitussives:*

# they help the cough remove its cause

These elegant antitussives comprise a group of significantly superior expectorants from which you may select the formula best suited for your coughing patient.

First of all, they have more in common than mere delectability to eye and palate: they all include *glyceryl guaiacolate*. This remarkable expectorant aids the coughing mechanism by increasing the secretion of Respiratory Tract Fluid,[1] which helps liquefy sputum,[1,3] makes bronchial and tracheal cilia more efficient,[1,2] and acts as a demulcent.[1,3-5] Through its effects, all four expectorants promote the natural purpose of the cough, which is to remove the irritants that cause it.[1,2]

In addition, the Robins antitussive armamentarium provides a choice of widely accepted drugs in various combinations with glyceryl guaiacolate for treating different kinds of coughs and associated symptoms. For antihistaminic effects, there is Dimetane® or prophenpyridamine; for bronchodilation and nasal decongestion, there are sympathomimetic agents; and for suppression of the "too frequent" cough, there is codeine or dihydrocodeinone.

**Robitussin®**

*Each teaspoonful contains:*

Glyceryl guaiacolate ..... 100 mg.

**Robitussin® A-C**

*Each teaspoonful contains:*

Glyceryl guaiacolate ..... 100 mg.
Prophenpyridamine maleate .. 7.5 mg.
Codeine phosphate ..... 10 mg.
*(exempt narcotic)*

**Dimetane® Expectorant**

*Each teaspoonful contains:*

Parabromdylamine maleate (DIMETANE) ..... 2 mg.
Glyceryl guaiacolate ..... 100 mg.
Phenylephrine HCl, USP ..... 5 mg.
Phenylpropanolamine HCl, NNR ..... 5 mg.

**Dimetane® Expectorant-DC**

*Each teaspoonful contains* the Dimetane Expectorant formula *plus* Dihydrocodeinone bitartrate, NF ..... 1.8 mg.
*(exempt narcotic)*

*References:* 1. Cass, L. J., and Frederik, W. S.: Am. Pract. & Digest Treat. *2*:844, 1951. 2. Blanchard, K., and Ford, R. A.: Journal-Lancet *74*:443, 1954. 3. Hayes, E. W., and Jacobs, L. S.: Dis. Chest *30*:441, 1956. 4. Blanchard, K., and Ford, R. A.: Rocky Mountain M. J., Vol. 52, No. 3, 1955. 5. Boyd, E. M., and Pearson: Am. J. M. Sc. *211*:602, 1946.

Robins

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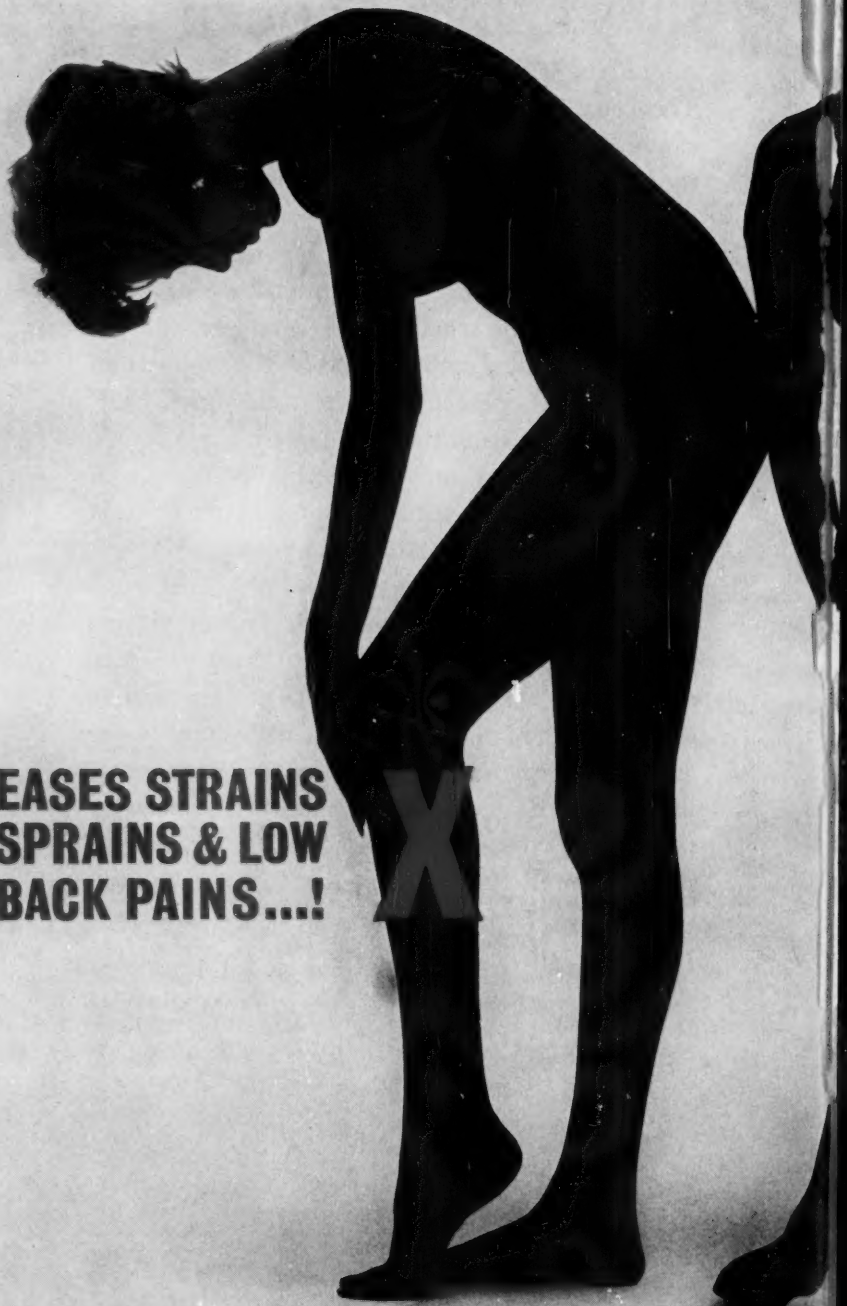
# ANNOUNCING SCHERING'S NEW MYOGESIC™



**RELA™** EASES STRAINS SPRAINS & LOW BACK PAINS...!

CARISOPRODOL

**RELA**—a new myogesic for better relaxant *and* analgesic therapy—more adept management of spasm and pain in strains, sprains and low back pains.

**RELA**—though a single drug—is a true myogesic and works rapidly to achieve three desired effects...

**Rela relaxes acute muscle spasm**
Relief of muscle spasm (96% excellent to good effectiveness)[1]

**Rela provides a unique quality of persistent pain relief through its relaxant and analgesic actions**
"Relief from pain was usually rapid and sometimes dramatic"[1]

**Rela, through relaxation and analgesia, assures daytime ease and nighttime rest**
"... A number of patients reported freedom from insomnia which they attributed to freedom from pain."[1]

**indications:** RELA is most beneficial in those conditions of the musculoskeletal system manifesting pain, stiffness and spasm.

**safety:** Studies of more than 1400 patients indicate that the toxicity of RELA is exceptionally low. In human subjects, respiratory, blood pressure or blood chemistry changes and/or renal, hepatic or endocrine dysfunction have not been reported.

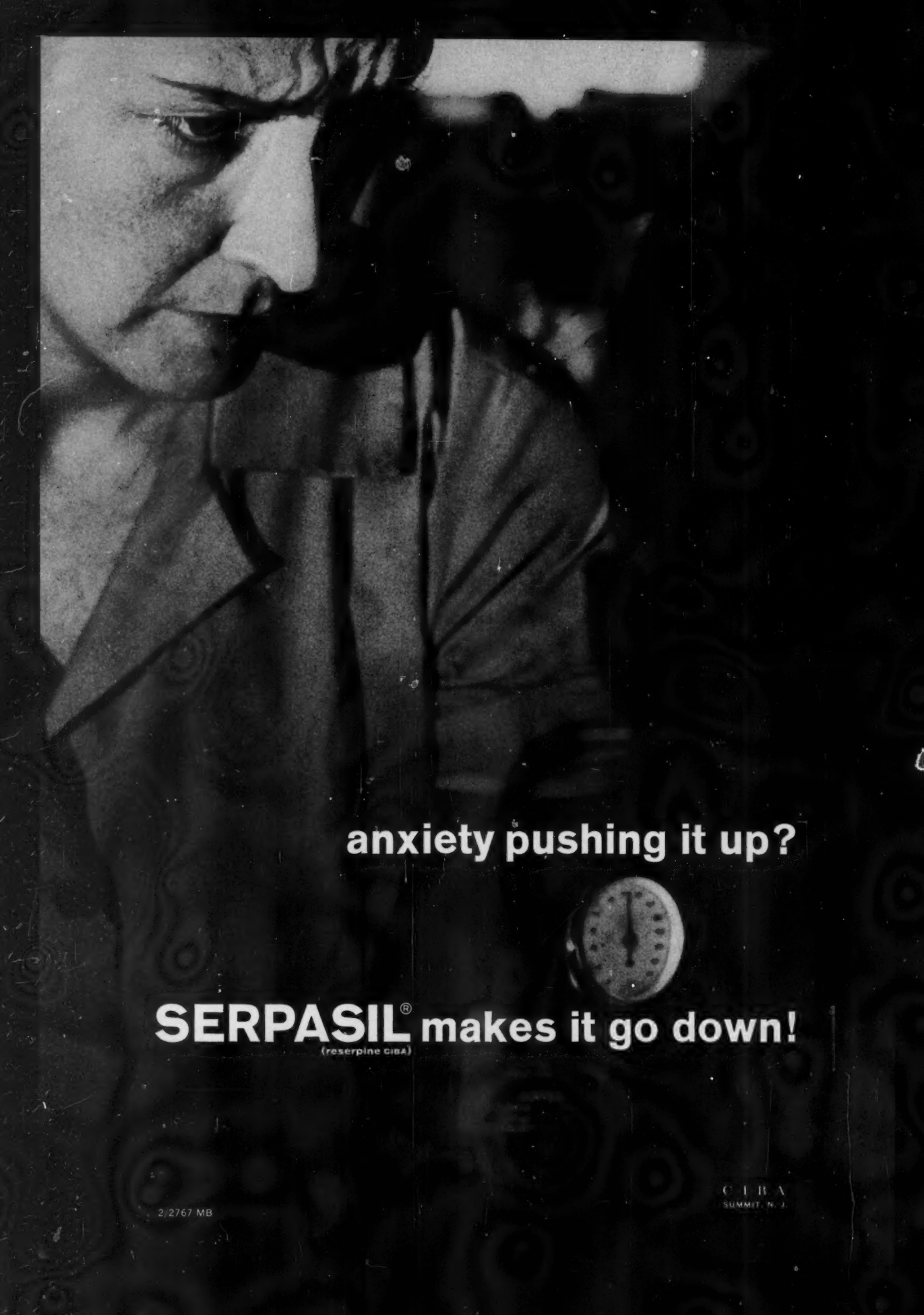
**dosage:** The usual adult dosage of RELA is one tablet 3 times daily and at bedtime. RELA has a rapid onset of action, with relief usually apparent within 30 minutes, and persisting for at least 6 hours.

**supply:** RELA is available as 350 mg., pink, coated tablets in bottles of 30.

1. Kuge, T.: To be published. M-227

**MYOGESIC**
*muscle-analgesic relaxant*

Schering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makes it go down!
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# Michigan Health Council Promotes Health Careers

The Michigan Health Council presented four regional health conferences during October and November to take information on health careers, the reduction of traffic accidents, and community, school and rural health programs to Michigan residents.

The conferences were held at Northern Michigan College, Marquette, October 29; Western Michigan University, Kalamazoo, November 5; Central Michigan University, Mount Pleasant, November 12, and McGregor Memorial Conference Center, Wayne State University, November 19.

More than 2,000 students from the host colleges and universities and from nearby high schools attended.

A total of 175 persons, representing the various health careers, appeared on the program or distributed literature and other information at desk side conferences and exhibits.

"Accidents, Ltd."—a separate session at each conference—took an interesting approach to reducing accidental injuries and deaths. Specially "incorporated" for the conferences, the corporation was made up of every Michigan citizen. Those taking part as speakers on this program included doctors of medicine, automobile manufacturing safety engineers, the state police, highway engineers, driver training directors, safety commission directors and newspaper and radio station executives. Each told of the assets and liabilities of their highway safety programs.

The Michigan Foundation for Medical and Health Education, Inc., through its president, E. I. Carr, M.D., Lansing, provided a special grant of $1,000 to assist the Michigan Health Council in sponsoring the regional conferences. Luncheons at Marquette, Kalamazoo, and Detroit were sponsored by the Oldsmobile Division of General Motors Corporation, the Upjohn Company, and Parke, Davis and Company, respectively. The Michigan National Bank again made a grant toward printing the preliminary program. Doctor Carl S. Winters, Oak Park, Illinois, was luncheon speaker at Mount Pleasant, and was sponsored by the General Motors Corporation.

## Michigan Pathological Society Radioactive Fallout

Man now has enough data to permit him to live safely in the atomic age, but he urgently needs more facts to live also effectively and economically, Shields Warren, M.D., told members of the Michigan Pathological Society December 12, 1959.

Undue risks should not be taken, nor should fear of hypothetical consequences be permitted to retard the atomic age.

Doctor Warren, who presented the fourth annual Carl V. Weller lecture, was the first director of the Division of Biology and Medicine of the U. S. Atomic Energy Commission and has written, extensively on tissue changes induced by radiation. A past president of the American Association of Pathologists and Bacteriologists, the American Society for Experimental Pathology, the American Association for Cancer Research, and the American Board of Pathology,



Doctor Warren is the recipient of the Ward Burdick Award, highest honor paid by the American Society of Clinical Pathologists. He is a professor of pathology at Harvard Medical School.

It should be brought out, Doctor Warren emphasized, that low-level exposure to radiation is not new to man, and that the human race since its origin has probably been exposed to background radiation of about 100 mr per year or more. In relation to radioactive fallout, over which there has been so much discussion, it is well to remember that present levels of radioactivity due to fallout are less than the increased hazard experienced by living in one city rather than another.

One reason that there is so much argument about fallout is that the full effects of radiation, even in large dosage, may be long in becoming apparent. Consequently, some feel that even slight amounts of radiation may have deleterious effects years hence. A vast amount of animal experimentation will be necessary to evaluate clearly such potential effects and it is possible they may never be fully evaluated, he stated, since the effects proposed may be less than those occurring spontaneously in different groups of control populations.

One of the puzzles to the pathologist as well as to other scientists is that the effect on a given organ or tissue is always manyfold greater than would be expected by the actual energy transfer, indicating that ionizing radiation must act on some key component of the cell, probably a nucleic acid complex by which damage can be effectively multiplied.

Interestingly enough, Doctor Warren pointed out, entire organisms are much more susceptible to radiation injury than are their component parts. Thus, irradiation of only those tissues in and about the cervix of the uterus has far less systemic effect than a tenth of that dose delivered to the organism as a whole. Similarly, isolated cells or cells growing in tissue culture can survive doses of radiation that would be lethal to them were they a component part of an organism wholly irradiated. The changes induced by total body radiation are largely determined by the response of the most sensitive tissues such as the hematopoietic system, germinal epithelium, and intestinal mucosa.

Doctor Warren stressed that the pathologist must familiarize himself with the picture of the delayed effects of radiation and learn the diagnostic criteria for radiation-induced change.

The Carl V. Weller lectures were established in 1956 by the Michigan Pathological Society to honor the professor of pathology at the University of Michigan Medical School. Previous Carl V. Weller lecturers were Howard T. Karstner, M.D., John C. Bugher, M.D., and E. T. Bell, M.D.

## Dates Set for New Michigan Conference

The First Annual Michigan Conference on Comparative Medicine will be held at Michigan State University March 21 and 22, sponsored by the Michigan Department of Health, the University of Michigan Medical School, the Wayne State University College of Medicine, and the Michigan State University College of Veterinary Medicine.

The conference planners contend that much benefit can be derived from an annual interdisciplinary conference at which information on diseases which man shares with the lower animals could be presented and exchanged. It was decided to undertake a series of such conferences and to choose a different central theme for each.

The program for this first conference will deal with the basic and comparative aspects of cancer

Although sponsored by Michigan institutions, the conference is expected to have nationwide appeal among those physicians, veterinarians, medical technologists, nurses, and other medical scientists who are interested in the cancer problem.

Inquiries about the program should be addressed to Michigan Conference on Comparative Medicine, Kellogg Center for Continuing Education, Michigan State University, East Lansing.

## Wayne State University Reunion

The Wayne State University College of Medicine Alumni Clinic Day and Reunion will be held May 4, 1960. That announcement was made by R. L. Mainwaring, M.D., at the recent meeting of the alumni association board of governors. Dr. Mainwaring will be chairman of the committee.

Wayne State University College of Medicine reports an enrollment this year of 371. Graduate student enrollment at Wayne is 5,018, while the total number attending Wayne is 20,510.

## Medical Meetings and Clinic Days

| *1960* | *Events* | *Location* |
|---|---|---|
| January 30-31 | County Secretaries—Public Relations Seminar | Detroit |
| February 13 | Maternal Health Day | Detroit |
| February 25-27 | National Conference on Rural Health | Grand Rapids |
| March 8-11 | Michigan Clinical Institute | Detroit |
| March 21-22 | Michigan Conference on Comparative Medicine | East Lansing |
| April 7 | Ingham County Spring Clinic | Lansing |
| April 13 | Genesee County Cancer Day | Flint |
| June 17-18 | Upper Peninsula Medical Society | Escanaba |
| July 28-29 | Coller-Penberthy Clinic | Traverse City |

MICHIGAN DEPARTMENT OF HEALTH
ALBERT E. HEUSTIS M.D., State Health Commissioner

## The Importance of Mass Screening Programs

EDITOR'S NOTE: *Each month, the State Health Commissioner is invited to express his views on health matters and Michigan Department of Health activities.*

Too much disease is discovered too late when too little can be done about it.

Unquestionably, there are not now, and perhaps there never will be enough physicians to provide periodic physical appraisals on a widespread basis. The extension of public mass screening programs is essential if we are to detect more persons who may have disease in early stages and encourage them to go to their physicians for examination and diagnosis.

Such testing programs are aimed at getting the person with possible disease to his doctor for diagnosis when there is the best chance to correct the condition, to postpone disability, or to use rehabilitation measures. These programs also serve as a springboard for meaningful health education.

They are not a substitute for periodic physical appraisals, but a necessary supplement to them. Furthermore, they conserve the physicians' time by bringing to him persons who are more likely to have diseases.

Historically, mass screening programs for the detection of certain diseases in children and young people have been widely accepted. But fundamentally, we, in the Michigan Department of Health, are as concerned about the early detection of cancer in a fifty-year-old or diabetes in a sixty-year-old as we are in the early discovery of vision or hearing defects in youngsters.

We believe there is a great need to use proven early detection weapons on a much larger scale. The early detection of disease through mass screening programs can and does save lives.

TABLE I. CERVICAL CANCER SCREENING PROJECTS

| County | Year of Project | Number Women Examined | Positive* | Suspect* | Atypical* | Number Followed | Proven Cases | Rate/ 1,000 |
|---|---|---|---|---|---|---|---|---|
| St. Joseph | 1954 | 1,018 | — | — | 130 | 127 | 3 | 2.9 |
| St. Joseph | 1955 | 1,323** | — | — | 48 | 19 | 2 | 1.5 |
| Saginaw | 1955 | 1,000 | — | — | 50 | 42 | 2 | 2.0 |
| Saginaw | 1956 | 300** | — | — | 24 | 23 | 3 | 10.0 |
| Copper Country | 1957 | 1,201 | 14 | 98 | — | 68 | 6 | 5.0 |
| Copper Country | 1958 | 653** | — | — | 15 | 4 | 0 | 0.0 |
| Macomb | 1957 | 759 | 6 | — | 41 | 35 | 5 | 6.6 |
| Oakland | 1958 | 1,278 | 14 | 19 | — | 36 | 8 | 6.3 |
| Jackson City | 1958 | 1,020 | 4 | 8 | — | 10 | 4 | 3.3 |
| | | 8,552 | 38 | 125 | 308 | 364 | 33 | 3.9 |

*Represents diffe-ing ways of reporting smear results.
**Largely rescreening surveys.

TABLE II. DIABETES SCREENING USING CLINITRON

| Location | Date | Number Screened | Number Suspect | New Cases | New Cases Per 1,000 | Cases Prev. Known |
|---|---|---|---|---|---|---|
| Dickinson-Iron | June 1957 | 5,564 | 55 | 16 | 2.9 | 12 |
| Montmorency | Jan. 1958 | 1,031 | 17 | 6 | 5.8 | 7 |
| Hillsdale | Feb. 1958 | 3,062 | 46 | 7 | 2.3 | 3 |
| Ingham | Mar. 1958 | 683 | 25 | 0 | | 13 |
| Gladwin-Arenac | May 1958 | 982 | 10 | 4 | 4.1 | 1 |
| Chippewa-Luce-Mackinac | June 1958 | 6,030 | 87 | 38 | 6.3 | 10 |
| Ionia Fair | Aug. 1958 | 1,122 | 16 | 2 | 1.8 | 4 |
| Detroit Fair | Sept. 1958 | 1,914 | 29 | 2 | 1.0 | 2 |
| Newberry State Hospital | Mar. 1959 | 1,593 | 23 | 20 | 12.6 | 0 |
| Saginaw City | Mar. 1959 | 5,799 | 51 | 22 | 3.8 | 8 |
| | | 27,780 | 329 | 117 | 4.2 | 60 |

For example, consider cancer of the cervix. For thirty years we have had the basic knowledge which would enable us to find this type of cancer early when the chance for recovery is very good. We have known about this method involving microscopic examination of cervical cells for thirty years, yet every month about thirty-five Michigan women die of cervical cancer, over 400 every year. Nationally, the figure runs in the thousands. Table I shows our experience in screening women for cervical cancer.

(*Turn to Page 64*)

# HEART BEATS

## Nutrition Program

The Nutrition Program of the Michigan Heart Association has emerged from pilot status to that of a full program. Instruction in the practical application of prescribed sodium restriction diets is given to patients and those preparing food for patients. Trial classes have proved satisfactory and the program has received the approval of the Michigan State Medical Society.

Classes will be arranged in Michigan Communities upon request. Information about arrangements may be obtained by writing to the Program Director, Michigan Heart Association, Doctors' Building, 3919 John R, Detroit 1, Michigan.

## New Booklet on Home Care

A new pamphlet, "Home Care of the Child with Rheumatic Fever," has been published by the American Heart Association and its affiliates. The 24-page, illustrated booklet offers parents some ideas on how to cope with a sick child. It was prepared for parents of youngsters for whom hospital treatment is either not advised nor available.

Issued as a companion piece to "Have Fun . . . Get Well," the Heart Association publications on recreational activities for the sick-abed, the new booklet contains basic information and hints useful in the care of sick children in general. It offers practical pointers on home nursing techniques and also includes suggestions for dealing with psychological and emotional problems that are likely to arise when a youngster is confined to bed for more than a week or two.

The booklet goes into detail about the role of the mother in caring for the sick child and the importance of following the regimen prescribed by the physician. Instruction is included on bathing the child in bed, giving medicine, taking the pulse and temperature and keeping records for the doctor. Choosing and preparing food for the sick child, planning a daily schedule for mother and child, and the use of home care equipment are also discussed.

Physicians and others may request copies of the pamphlets by writing to the Detroit office.

## ECG Test Books

Electrocardiographic Test Book Sets are still available. The set is in two volumes. Volume I contains Part A, Electrocardiograms with Questions; Part B, Questions on Electrocardiographic Interpretation; An Appendix of tables useful in electrocardiographic interpretation, and the Index to both volumes. Volume II is also divided into Parts A and B. Answers to the questions and detailed discussion of the tracings presented in Volume I are on the corresponding pages in Volume II.

In addition to the answers to the questions, supplementary clinical information, x-rays, and serial electrocardiograms are presented. The cost of the complete set is $5.00 postpaid.

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# Michigan Department of Health

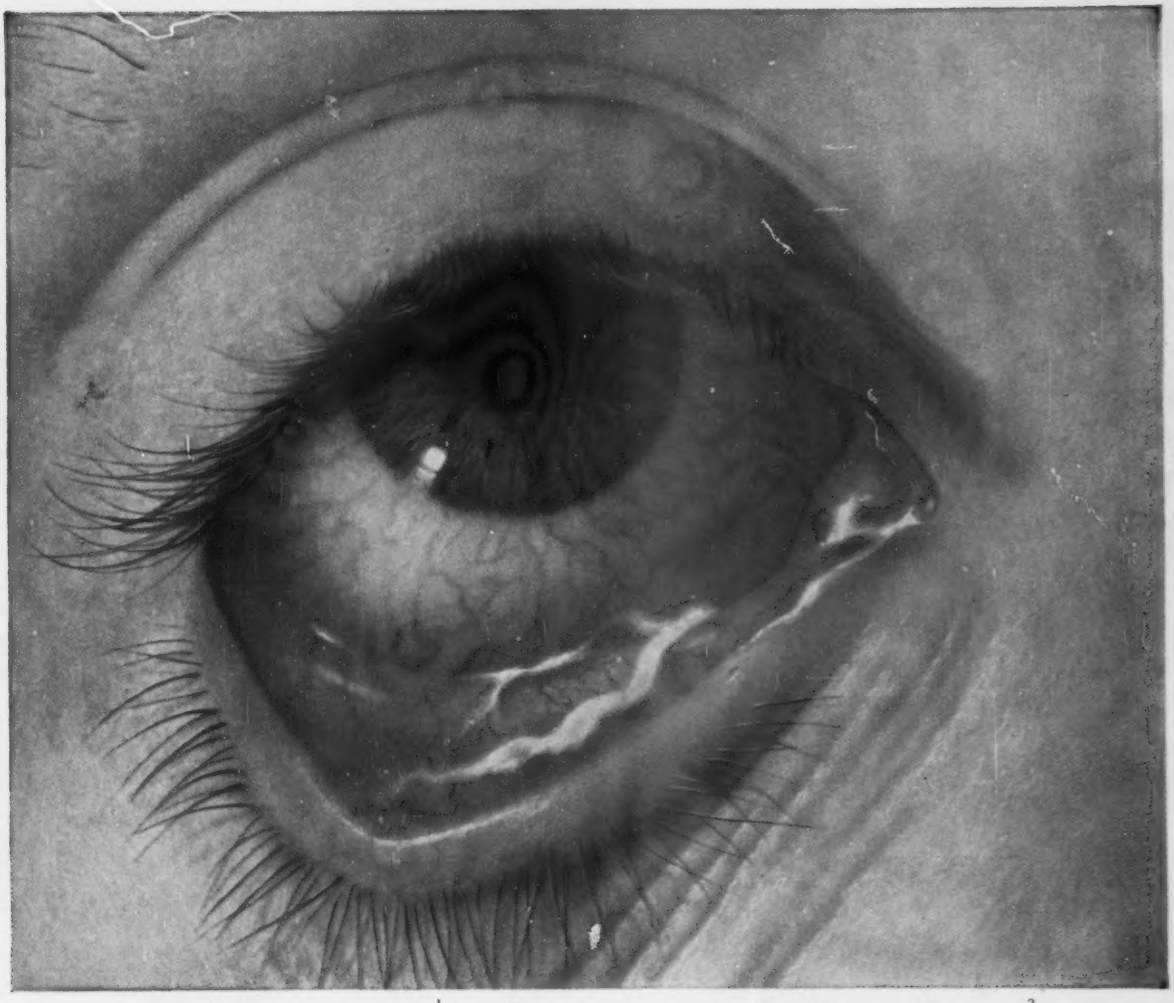
## The Importance of Mass Screening Programs

*(Continued from Page 63)*

We have screened less than 9,000 women in organized programs. The rate of proved cases is about four out of every thousand women examined, potentially one life saved out of every 250 tested. In all of these programs, specimens were taken by private physicians but the cost was reduced for the individual by subsidizing the laboratory work with federal funds. In most cases, an attempt was made to concentrate on women in the age group in which this type of cancer strikes most frequently.

Another example is diabetes. Because of its hereditary nature, diabetes is becoming, and will continue to become, more widespread year after year. Since diabetes is a progressive disease, it is important to find it early when there is a good chance to prevent complications. Again through federal funds, a number of diabetes screening projects have been sponsored by the state and local health departments with the assistance of local physicians. Table II shows our experience in these screening programs using the clinitron. The rate of discovery is more than four previously unknown cases out of every 1,000 persons tested.

These are only two examples of mass screening programs which without question can and do save lives. Mass screening programs represent one of the newer phases of the long-established partnership between private medicine and public health which is founded upon mutual trust and a common interest in the health and welfare of American people.



no irritating crystals[1] · uniform concentration in each drop[2]

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"The solution of prednisolone has the advantage over the suspension in that no crystalline residue is left in the patient's cul-de-sac or in his lashes . . . . The other advantage is that the patient does not have to shake the drops and is therefore sure of receiving a consistent dosage in each drop."[2]

1. Lippmann, O.: Arch. Ophth. **57**:339, March 1957.
2. Gordon, D.M.: Am. J. Ophth. **46**:740, November 1958.

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*on the alcoholic scene*

# Vistaril®

quiets agitation

*hydroxyzine pamoate*

*"... an efficient and convenient means of dealing with the problem of acute agitation in alcoholic intoxication . . . important was the absence of noticeable respiratory depression. . . ."*

Miller, R. F.: Clin. Rev. 1:10 (July) 1958

Capsules—25, 50, and 100 mg.
Parenteral Solution (as the HCl)— 25 mg. per cc., 10 cc. vials and 2 cc. Steraject® Cartridges; 50 mg. per cc., 2 cc. ampules.

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# Lifts depression....

**An emotionally balanced patient**
Thanks to your treatment and the help of Deprol, her depression is relieved and her anxiety and tension calmed. She eats well, sleeps well, and can return to her normal activities.

# as it calms anxiety!

## Deprol helps balance the mood by lifting depression as it calms related anxiety

*No "seesaw" effect of amphetamine-barbiturates and energizers*

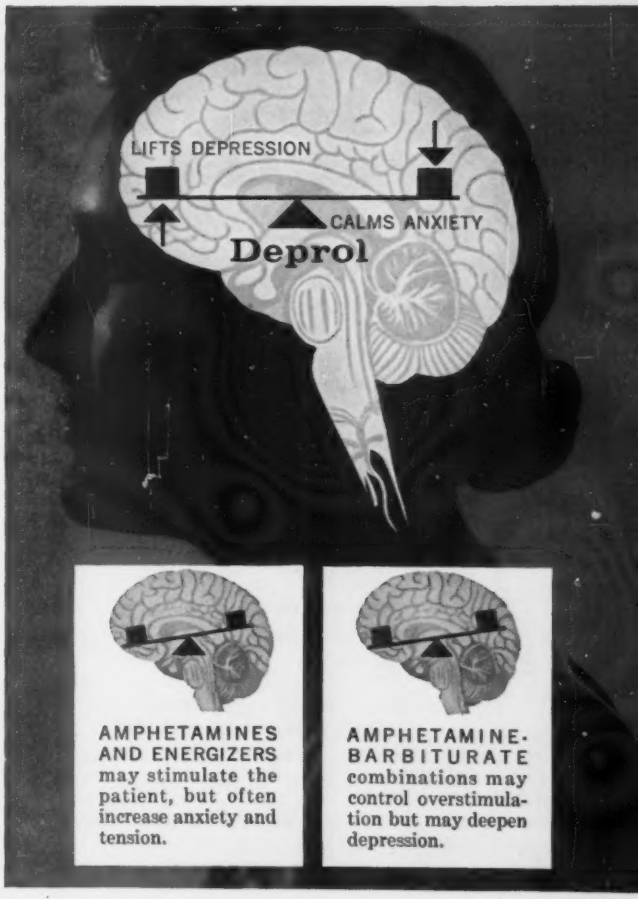
While amphetamines and energizers may stimulate the patient—*they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation—*they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety—both at the same time.

*Safer choice of medication than untested drugs*

Deprol does not produce hypotension, liver damage, psychotic reactions or changes in sexual function.

**BIBLIOGRAPHY:** 1. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. 2. Bateman, J. C. and Carlton, H. N.: Deprol as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy. In press, 1959. 3. Bell, J. L., Tauber, H., Santy, A. and Pulito, F.: Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. 4. McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B.: Treatment of depression—New technics and therapy. Am. Pract. & Digest Treat. In press, 1959. 5. Pennington, V. M.: Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. 6. Rickels, K. and Ewing, J. H.: Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. 7. Ruchwarger, A.: Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. 8. Settel, E.: Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy. In press, 1959.

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**SUPPLIED:** Bottles of 50 light-pink, scored tablets. Write for literature and samples.

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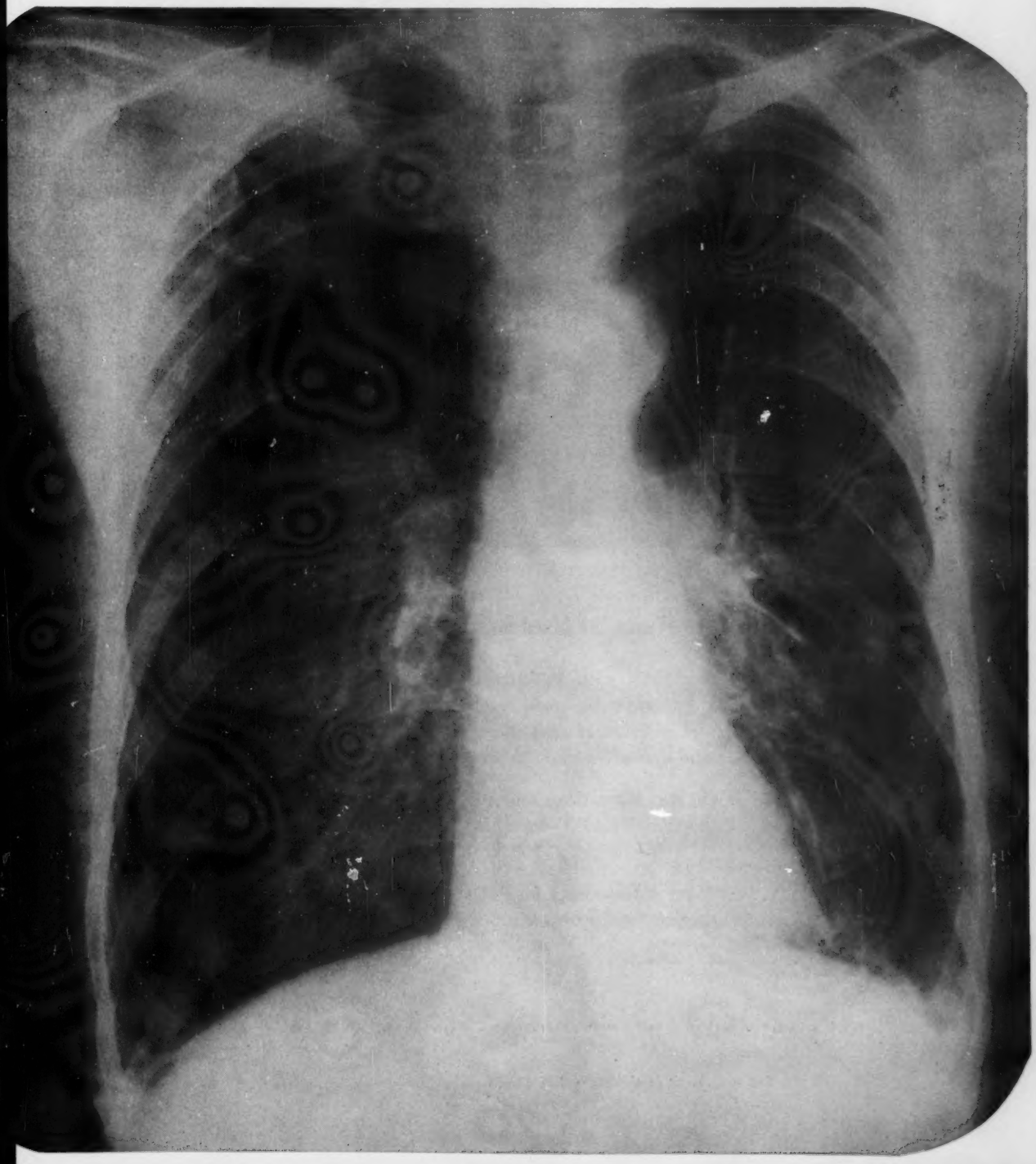

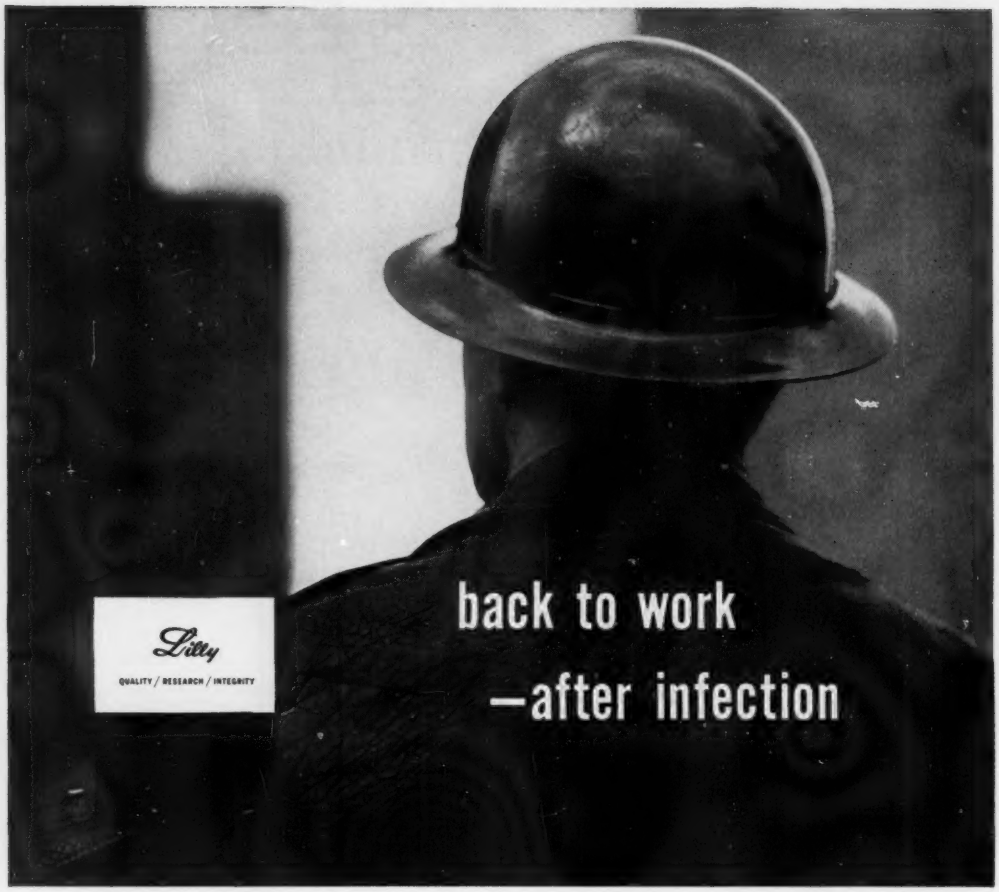


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Dosage: 125 or 250 mg. three times daily. Supplied as scored tablets of 125 and 250 mg. (200,000 and 400,000 units).

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V-Cillin K, Pediatric: A taste treat for young patients. In bottles of 40 and 80 cc. Each 5-cc. teaspoonful provides 125 mg. of V-Cillin K.

V-Cillin K® (penicillin V potassium, Lilly)

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# Surgical Treatment of Ventricular Septal Defects

**Conrad R. Lam, M.D.**
**Detroit, Michigan**

IN 1954, Lillehei and his associates[4] at the University of Minnesota by-passed the heart by cross circulation with a human donor and demonstrated that closure of ventricular septal defects under direct vision is feasible. Fortunately, the human donor method for by-passing the heart was soon replaced by a simple and inexpensive mechanical oxygenator of the bubble type.[5] In the meantime, Kirklin and his associates at the Mayo Clinic[2] had used successfully an oxygenator of the Gibbon type for the closure of ventricular septal defects.

Obviously, the feasibility of this type of intracardiac surgical procedure is definitely established. However, there has been ample opportunity for further refinements. First of all, the operative field is far from dry because, with the conventional by-pass, only the vena cavas are occluded; and the heart is allowed to beat, with the result that there is a continuous flow of coronary sinus blood into the right ventricle through the tricuspid valve. Also, there may be a serious back-flow of blood from the aortic valve because of structural or functional insufficiency as a result of distortion. The motion of the beating heart is not conducive to the meticulous kind of suturing which is indicated for the complete and permanent closure of the septal defect which lies in such a critical area in proximity to the conduction bundle and the aortic valve. The answer to all of these problems lies in the principle of induced cardiac arrest.

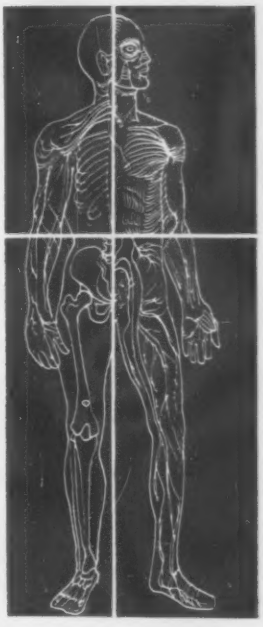
At the 1955 meeting of the American Association for Thoracic Surgery, some investigations supported by the Michigan Heart Association were reported.[3] The heart was stopped with the injection of potassium chloride into the left ventricle. With the brain protected by hypothermia, complicated operations were carried out in the auricles and ventricles. Since no pump-oxygenator was available at that time, we had to depend on manual systole to expell the potassium salt from the coronary arteries and ventricular fibrillation was a common complication. However, in a series of twenty animals, only one had refractory fibrillation. In November 1955, we began some tests with acetylcholine as the cardioplegic drug and found that it was excellent for the purpose. In the meantime, Melrose[6] of London demonstrated that potassium citrate is useful for inducing cardiac arrest and this method has been applied clinically by Effler and his associates.[1]

---

From the Division of Thoracic Surgery of the Henry Ford Hospital, Detroit, Michigan.

Presented in the Panel on Cardiac Surgery, Michigan Clinical Institute, Detroit, March 12, 1959.





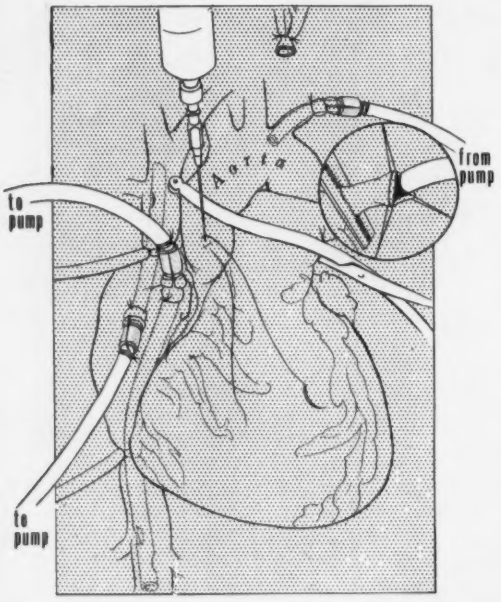



Fig. 1. Diagram of cannulations for by-passing the heart with the pump-oxygenator, and method of inducing cardiac arrest by the injection of acetylcholine. The femoral artery is now used almost exclusively for the return of oxygenated blood rather than the left subclavian.

## Method

The chest is opened through a transverse incision through the third interspace and the sternum. After heparinization of the patient, a systemic artery (usually a femoral) and the vena cavas are cannulated (Fig. 1) and attached to the appropriate outflow and inflow tubes of the pump-oxygenator system (Fig. 2). When a test—with the pump running—shows that the inflow and outflow are balanced, a non-crushing clamp is placed across the aorta (and also the pulmonary artery for reasons of convenience) and acetylcholine in the amount of 10 mg./kilo. of body weight is injected into the aorta proximal to the clamp. The drug enters the coronary arteries and promptly stops the heart. An incision is then made in the outflow tract of the right ventricle and the defect is exposed.

THE AUTHOR

Conrad R. Lam, M.D.

In a fair number of cases, it will be necessary to divide one or more papillary muscles so that the septal tricuspid leaflet may be retracted better. The common type of high defect is shown in Figure 3. Closure is effected by placing interrupted sutures which are tied over a pledget of Ivalon sponge. No recurrence of the defect has been noted following this type of closure.

As soon as the intracardiac part of the operation has been completed, the heart is started by removing the aortic clamp. This permits the perfusion of oxygenated blood through the coronary arteries and

Fig. 2. Pump-Oxygenator of the bubble type (Lillehei-DeWall) which has been used to permit the open heart operations in this series.

the acetylcholine is washed out. The blood which is rich in the cardioplegic drug passes out of the coronary sinus, through the tricuspid valve and into the open right ventricle, where it escapes during the closure of the incision into the right ventricle. As a rule, an excellent heart beat is present by the time the ventricular suture line is finished. The cannulas are then removed from the vena cavas and subclavian artery, and protamine sulfate solution is injected to neutralize the heparin. A few sutures are placed in the pericardium and the chest is closed with drainage tubes in both thoracic cavities.

The postoperative care of patients who have had repair of interventricular septal defects is exceedingly important. Postoperative hemorrhage must be watched for diligently and treated appropriately by blood replacement, additional protamine and, if necessary, exploration of the chest and pericardium. The main-

tenance of a clear airway may be difficult and the use of prophylactic tracheotomy in infants under the age of one year has much to commend it.

## Results

At the time of the preparation of this report (November 1, 1959) 158 operations for the cure of ventricular septal defect have been carried out on 156 patients (two patients were operated on a second time because of early recurrence of the defect). There were forty-one deaths in the entire series, giving a mortality rate of 26 per cent. Less than half of the infants under the age of one year survived. In patients over the age of three years, the mortality rate was 13 per cent.

We have accepted many cases with marked pulmonary hypertension for operation. The important thing is whether the pulmonary hypertension is due primarily to flow or resistance of the vascular bed of the lung. Increased pulmonary flow is revealed by elevation of the pulmonary capillary wedge pressure or the pulmonary vein pressure, x-ray evidence of increased pulmonary vascularity and electrocardiographic evidence of left atrial and ventricular enlargement. Resistance as the predominant factor is evidenced by pulmonary artery hypertension in the absence of parallel elevation of wedge pressure or pulmonary vein pressure, decreased pulmonary vascularity and electrocardiographic indication of predominantly right heart enlargement. The fact that there were five survivals in the ten cases in which the pulmonary artery pressure was equal to that of the aorta was probably because no cases of balanced shunt with marked pulmonary resistance and little or no flow were accepted for the operation.

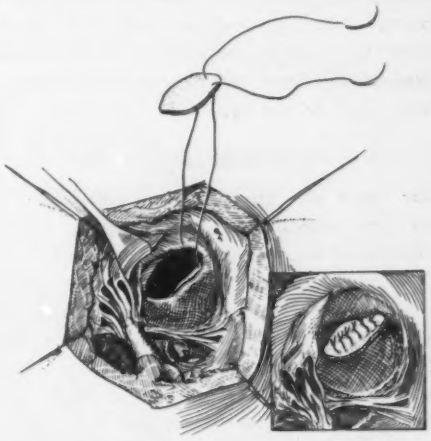


Fig. 3. Exposure of the ventricular septal defect and method of closure with sutures tied over a patch of Ivalon sponge. Note that the sutures are passed through the fibrous tissue of the left ventricular side of the septum rather than the muscular tissue on the right side, to avoid conduction bundle injury.

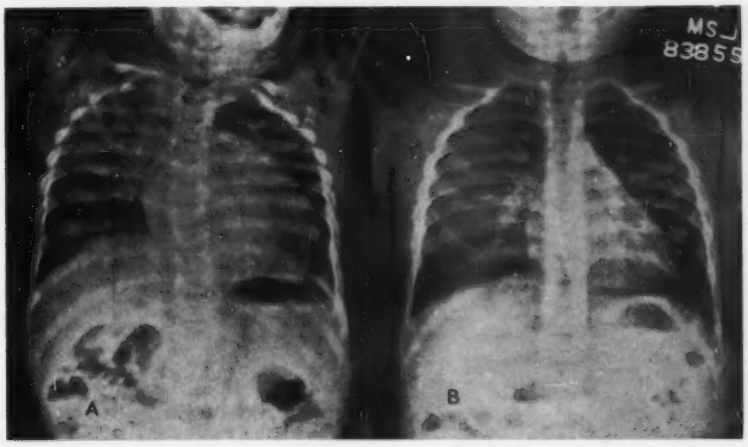



Fig. 4. (a) Roentgenogram of the chest of infant one year of age with evidence of ventricular septal defect. Note the globular heart and the increased vascularity of the lungs. (b) Roentgenogram of chest five months following closure of the septal defect. The change in the shape of the heart, and the decreased vascularity of the lungs are striking.

There have been no late deaths or serious complications in the patients who have lived more than two days after the operation, with the exception of two instances of early recurrence. The clinical improve-

ment following the closure of the shunts has been remarkable. Weight gain in the undernourished children has been rapid. The cardiac status has promptly changed into a normal one. Normal activity has been tolerated within the first few weeks. A surprising dividend has been the rapid change of the radiologic picture of the heart toward one that is essentially normal (Figs. 4a and b).

## Summary

The repair of ventricular septal defects is a relatively safe surgical procedure, provided reasonable candidates for the operation are selected and the technical details of the operation are carefully managed. The poorest results will be obtained in very young infants (under the age of one year) and in patients with high pulmonary arteriolar resistance. The best results will be obtained in children above the age of three years and in those patients with high pulmonary artery flows.

Induced cardiac arrest with acetylcholine as the cardioplegic agent is a valuable adjunct during the cardiac by-pass with the pump oxygenator.

## References

1. Effler, D. B., Groves, L. K., Sones, F. M., and Kolff, W. J.: Elective cardiac arrest in open-heart surgery. Report of three cases. Cleveland Clin. Quart., 23:105, 1956.

2. Kirklin, J. W., DuShane, J. W., Patrick, R. T., Donald, D. E., Hetzel, P. S., Harshbarger, H. G., and Wood, E. H.: Intracardiac surgery with the aid of a mechanical pump-oxygenator system (Gibbon type): Report of eight cases. Proc. Staff Meet., Mayo Clin., 30:201, 1955.

3. Lam, C. R., Gahagan, Thomas, and Lepore, Alfredo: Induced cardiac arrest for intracardiac surgical procedures. J. Thoracic Surg., 30:620, 1955.

4. Lillehei, C. W., Cohen, Morley, Warden, H. E., Ziegler, N. R., and Varco, R. L.: The results of direct vision closure of ventricular septal defects in eight patients by means of controlled cross circulation. Surg., Gynec. & Obst., 101:446, 1955.

5. Lillehei, C. W., DeWall, R. A., Read, R. C., Warden, H. E., and Varco, R. L.: Direct vision intracardiac surgery in man using a simple, disposable artificial oxygenator. Dis. Chest., 29:1, 1956.

6. Melrose, D. G., Dreyer, B., Bentall, H. H., and Baker, J. B. E.: Elective cardiac arrest. Lancet, 2:21, 1955.

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## Continuing Dangers of Tuberculosis

"The public has become over-optimistic. Many people are not even vaguely aware of the continuing dangers of tuberculosis in their communities," says the 1959 Annual Report of the National Tuberculosis Association.

The report also states:

"With every fourth person carrying tuberculosis germs, one never knows when or where the hidden enemy will strike.

"The total number of cases is not declining rapidly.

"One fourth of the known active cases at home have no medical supervision."

The NTA urges a three-point attack against the disease—detection, treatment, and research. National statistics place tuberculosis as the most serious infectious disease problem in the country. The NTA report cites 83,000 new cases and 12,000 deaths reported in a year; 150,000 patients known to have active tuberculosis; 100,000 or more persons with unknown active tuberculosis; and 1,750,000 former patients who should be kept under medical and public health supervision.

# Clinical Hyperthyroidism and Coarctation of the Aorta

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SINCE the original article by Paris[10] appeared in 1791, the interest of physicians regarding coarctation of the aorta has been maintained to the present day. Through the nineteenth century and the early part of the twentieth, such names as Cooper, Meckel, Laennec, Minkowski, Rokitansky, Monckeberg, Abbott, and Lewis have appeared in the literature in connection with original thought and study on the subject. Work by various men during the past decade has, naturally enough, stressed the techniques of diagnosis and surgical correction of the lesion—previously often overlooked, and not amenable to repair when discovered.

Prior to the advent of effective surgical treatment and antibiotics, early writers confined their interest to the morbid anatomy of the condition. The history and pathogenesis of the lesion have been admirably covered in the classic works of Abbott[1] and Blackford[3]; little can be added to their work, done some thirty years ago. Maire's observations present several theories regarding etiology. He concluded that arteriosus stenosis with incorporation of the contiguous portion of the aorta and/or embryonic maldevelopment of the descending limbs of the primitive left aorta were logical choices.

The physiologic results of this maldevelopment have been extensively studied in recent years—newer techniques of experimentation are providing valuable information regarding hemodynamics of the various organs, and advances in radiography are providing a more precise diagnosis of the lesion in any individual case.

Prognosis has advanced along with diagnosis and treatment in cases amenable to surgery; the majority of Abbott's cases died before their fortieth year, usually suddenly because of ventricular rupture or infarction, or, in a matter of days, because of bacterial endocarditis and heart failure. Recently, antibiotics and control of hypertension have further added to the effectiveness of surgical treatment.

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The literature over the years abounds with reports of coarctation in conjunction with other congenital anomalies, usually of the cardiovascular system. One may logically presume that physiologic alterations, as well as anatomic changes, are to be expected in patients who harbor the coarctation. Among these changes, hyperthyroidism has been previously mentioned by a number of workers from time to time. Loriga[8] first mentioned hyperthyroidism, or Flajani's disease, with aortic coarctation. Amberg[6] cited a case of exophthalmic goiter in a thirteen-year-old girl; the aortic lesion was discovered three years after antithyroid treatment was begun. Ulrich[11] reported two cases first presented as hyperthyroidism: surgical removal of the gland was accomplished without results, and treatment with Lugol's solution was likewise futile. Eppinger and Midelfart[7] described two further cases. Brown[5] reported a patient with symmetrical enlargement of the thyroid gland who subsequently died of endocarditis. Cookson[6] mentioned a case wherein Lugol's solution was given without benefit; but total thyroidectomy was performed with relief of symptoms. A histologic study of this thyroid suggested hyperactivity of the glandular tissue, with low cuboidal epithelium and vacuolated colloid. Vascularity was markedly increased, and this feature of hypervascularity was postulated by Ulrich and later by Bramwell[4] as being the factor responsible for thyroid hyperactivity. Ulrich suggested ligation of the inferior thyroid artery for this reason. Bramwell, reporting on his twenty-six collected cases of aortic coarctation, noted "undue breathlessness, palpation, and fatigue in the majority of cases."

THE AUTHORS

John E. Finger M.D. *(left)*

Peter E. Tuynman, M.D. *(right)*

This paper will report the cases of aortic coarctation diagnosed at Mount Carmel Mercy Hospital from 1950-1956 (seven cases) and will comment upon the finding of clinical hyperthyroidism in three of these cases. This adjective must be used because radioactive iodine studies and serum protein-bound iodine values were not performed on these patients. In two of the three cases of this group, the hyperthyroidism persisted following resection of the coarctation until antithyroid drugs were used.

Two of these cases were seen by one of the authors (P.E.T.) and the other was diagnosed as hyperthyroidism clinically during the first examination at the hospital. Another case was one of Turner's syndrome, but clinical hyperthyroidism was absent and no studies were carried out. Within the past year, a student nurse with coarctation (seen by J.E.F.) was found to have an elevated basal metabolic rate of +19 and lowered serum cholesterol, but was suffering from endocarditis when these studies were done. (Follow-up studies after antibiotic therapy were normal.) A sixth case was a neonatal death, and a seventh was that of a fifteen-year-old girl who died of a subarachnoid hemorrhage, secondary to aneurysmal rupture. The diagnosis of aortic coarctation had been made by exploratory thoracotomy at age four. No mention of her thyroid status was available.

Although this series is small (only one case was noted when the more precise aids to the study of the thyroid gland were available), the fact that clinical hyperthyroidism was present in three out of six adult patients seems more than fortuitous, and bears out some of the previous observations on this subject.

## Case Summaries

*Case 1.*—D. W., white man, aged forty-one, was first examined on February 1, 1951, with complaints of recurring headaches and increasing fullness of the supraclavicular spaces and lower neck, and nocturia. Ten years previously, he had been diagnosed as possessing coarctation of the aorta but was deemed a poor surgical risk because of his age and the surgical techniques employed at that time.

Physical examination revealed the blood pressure in both arms to be 210 systolic, 110 diastolic. No blood pressure could be obtained in either leg. The temporal and cervical arteries were prominent and visibly pulsating. A notable precordial heave was present, as well as a grade II apical systolic murmur. The lower legs and feet were pale, cool and without palpable pulsation. The patient's weight at this time was 158 pounds.

The patient was admitted to Mount Carmel Mercy Hospital for further studies which confirmed the diagnosis of coarctation of the aorta. However, no thyroid function studies were performed at this time. Renal function tests proved normal, although incipient renal failure had been suspected.

The patient was operated upon on April 3, 1951. Resection was performed of a nearly complete coarctation situated 1.5 cm. distal to the left subclavian artery. Immediately following surgery, moderate pulmonary edema occurred, but responded to therapy.

As early as the fifth postoperative day, a wide pulse pressure was noted, the blood pressure being 170 systolic, 90 diastolic.

The increased pulse pressure and pulse rate of 90 to 110, persisted for some months after discharge from the hospital.

It was noted that persistent prominence of the lower anterior cervical area was caused by uniform enlargement of the thyroid gland. The patient complained of nervousness.

Basal metabolic rate on repeated determinations disclosed maximum figures of +25 per cent and +27 per cent. Antithyroid drug therapy utilizing propylthiourocil was instituted on November 3, 1951. This drug was continued in doses of 150 to 300 mg. daily for a period of fourteen months before complete subsidence of all signs and symptoms and lowering of the basal metabolic rate to normal limits was accomplished. At this time the patient's weight, which was 140 pounds upon discharge from the hospital, had reached 170 pounds.

*Case 2.*—W. B., aged thirty, was examined on January 3, 1952. His complaints were severe pounding headaches, soreness about the neck and upper chest, paresthesias of the legs and recent loss of equilibrium and ataxia.

Examination revealed blood pressure in both arms to be 220 systolic, 100 to 120 diastolic. Blood pressure in both legs was 90 systolic, 60 diastolic.

This man was admitted to Mount Carmel Mercy Hospital on January 11, 1952, for further studies and evaluation for resection of the coarctation. Cardiovascular and roentgenologic procedures confirmed the diagnosis of coarctation of the aorta.

Basal metabolic rate prior to surgery was +20 per cent. Serum cholesterol level was 115 mg. per cent. It was speculated at this time that the increased metabolic rate and the lowered serum cholesterol might be due to increased vascular pressure and flow in the pituitary or thyroid gland, or both, secondary to the aortic coarctation.

Resection of the coarctation was performed on January 22, 1952, and the patient made an uneventful recovery. The patient was discharged from the hospital on February 2, 1952, at which time his weight was 130 pounds.

The patient next appeared for examination on September 13, 1952, complaining of nervousness. At this time, the thyroid gland was palpable. The blood pressure was 160 systolic, 100 diastolic. Basal metabolic rate was +21 per cent. Antithyroid therapy employing Tapazole,* 25 mg. daily, was begun. On October 30, 1952, the patient still complained of nervousness and the blood pressure was found to fluctuate from 160 systolic, 90 diastolic, to 200 systolic, 120 diastolic.

Thereafter, the patient was not seen for twenty-six months, by which time he exhibited no evidence of hyperthyroidism and had gained seven pounds in weight, although he had long since discontinued the antithyroid drug.

*Tapazole, (Methimazole); Eli Lilly & Company (1-Methyl-2-Mercaptoimidazole)

*Case 3.*—B. F., a twenty-two-year-old white woman, entered the hospital on January 12, 1954, complaining of high blood pressure, diplopia, and mild exophthalmos for two to three years. Within the previous year she had noted heat intolerance, nervousness, and a 44-pound weight loss despite increased appetite. During the six months prior to admission she also became aware of shortness of breath on exertion, chest pain with exertion, and frontal headaches. Past history and systemic review were negative. Physical examination revealed facial flushing, mild exophthalmos, a prominent systolic thrill over both carotid arteries, and a prominence of the thyroid isthmus. In addition, the heart was enlarged to the left anterior axillary line. Blood pressure was 175 systolic, 95 diastolic and there was a harsh systolic murmur during the entire period of systole which was heard over the precordium and neck. Pulsation and blood pressure were absent in the legs.

The chest film showed rib notching and cardiomegaly. Urinalysis showed 2-plus albuminuria. Serum cholesterol was 253 mg. per cent and the basal metabolic rate was +14 per cent. Blood chemistry and electrocardiogram were within normal limits.

On January 22, 1954, the coarctation was resected. A 2 cm. segment of coarctated area distal to the left subclavian was removed.

The patient did well postoperatively, except for minor pleuritis and effusion in the left base. She was discharged on February 10, 1954, and has remained well to date, with blood pressure within normal limits. She was seen as an obstetrical patient about a year after surgery, and required no antithyroid treatment prior to surgery, or after it. In this case, the clinical criteria of hyperthyroidism were so well filled that the impression of the original examiner did not include aortic coarctation until the day after admission, when femoral pulses were noted to be absent.

## Comments

Although the tests employed did not include those developed more recently for thyroid evaluation, the authors feel that the signs of clinical hyperthyroidism present in three of the six adults were enough to confirm reports already cited in the literature of this condition as related to aortic coarctation. Cookson, Ulrich, and Bramwell postulated increased vascularity of the gland *per se* as the etiology for its hyperactivity. This would seem to be confirmed by the histologic examination of the tissue removed from Cookson's patient.

We would like to add another thought—that excess thyrotropic hormone, possibly due to increased pituitary vascularity, may be a factor to consider. Thyrotropic hormone usually provokes hypertrophy and hyperplasia of the thyroid epithelium, and the weight of the gland increases despite loss of colloid. Associated with the histologic change is an increased ability of the gland to take up iodine and synthesize thyroxin. However, the hormone is not stored but is immediately released to the circulation. It is suggested that in the investigation of persons harboring aortic coarctation, blood assays for thyroid-stimulating hormone, radioactive iodine uptake studies and protein-bound iodine determinations be performed. These procedures will denote the status of the thyroid gland and indicate whether it has been affected by the altered hemodynamics associated with coarctation of the aorta.

The authors feel that this association may occur more frequently than has been suspected and that it explains some instances in which elevated systolic pressure persisted following resection.

## Summary

The relationship of hyperactivity of the thyroid gland seen in some cases of aortic coarctation is presented. Literature is reviewed on this subject. The possible etiology of altered hemodynamics including increased vascularity of the gland as the etiology is considered, as well as the possibility of excessive production of thyrotropic hormone by the pituitary. Of six adult cases of aortic coarctation at Mount Carmel Mercy Hospital from 1950-1956, three had signs of clinical hyperthyroidism.

## References

1. Abbott, Maude E.: A statistical study and historical retrospect of 200 recorded cases, with autopsy, of stenosis or obliteration of the descending arch in subjects above the age of two years. Am. Heart J., 3:574-618, 1928.
2. Amberg, S.: Diagnosis and treatment of coarctation of the aorta of adult type in childhood. Libman Anniv. (Mayo Clinic), 1:55, 1932.
3. Blackford, L. Minor: Coarctation of the aorta. Arch. Int. Med., 41:702, 1928.
4. Bramwell, C.: Coarctation of the aorta, clinical features. Brit. Heart J., 9:100-127, 1947.
5. Brown, J. W.: Coarctation of the aorta with infective endocarditis. Lancet, 2:924, 1934.
6. Cookson, H.: Coarctation of the aorta with toxic goiter treated by complete thyroidectomy. Lancet, 2:623, 1936.
7. Eppinger, E. C., and Midelfart, P. A. H.: Stenosis of the isthmus (coarctation) of the aorta. Am. J. Med. Sc., 185:528, 1933.
8. Loriga, G.: Stenosis ed obliterazione congenita dell' aorta (coarctation) of the aorta. Rev. Clin., Bologna, 3d series, 7:529, 1887.
9. Maire, Edward D.: Coarctation of the aorta—review and a report of a case. New England J. Med., 236:1 (Jan. 2) 1947.
10. Paris: Cited by Abbott.[1]
11. Ulrich, H. L.: Coarctation of the aorta (adult type)—a report of three cases. Am. Heart J., 7:641, 1932.

# Congenital Arteriovenous Communication as a Posterior Mediastinal Tumor

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MANY cases of congenital arteriovenous communication have been reported in the medical literature.[1,2,5] The recent article by Fisher and Johnson of Denver, Colorado[4] seems to be the most comprehensive coverage of the subject for it discusses nine cases of congenital A-V communication of various locations. Fisher and Johnson emphasize the difficulty of correct histopathologic diagnosis of A-V communications because of their strong resemblance to hemangiomas and, therefore, being mistakenly diagnosed as such. Although A-V communications may be located anywhere on the body, reports of cases of the skin and extremities are more frequent than those of the inner organs. The explanation for this disproportionate recording may be advanced as resulting from the lack of clinical symptoms in all cases of A-V communication. The external cases are noted more easily than the internal ones, and one has reason to suspect that many of the internal A-V communications go unnoticed unless discovered by some chance such as the case to be reported.

The following aspects of our case make it different from the Beno and Das[2] report and interesting to discuss on its merits: (a) the patient had no clinical symptoms; (b) the diagnosis had to depend heavily on the x-ray findings thus arousing the question of its being a tumor of neurogenic origin; (c) the case may be the first A-V communication of this location to be reported.

## Report of Case

B. F. No. (A-30672), a white man, aged forty-seven, was admitted to Highland Park Hospital as a result of a routine chest x-ray which revealed a mediastinal tumor. The patient did not have any physical symptoms except for the history of a little weight loss which occurred after he had been notified of the findings of his chest x-ray. This may be attributed to the anxiety caused in the patient by the report. He gave no family history of cancer, diabetes or tuberculosis. He stated that he had been turned down by the army in 1942 for symptoms of tuberculosis but that his family doctor was unable to confirm these findings at the time.

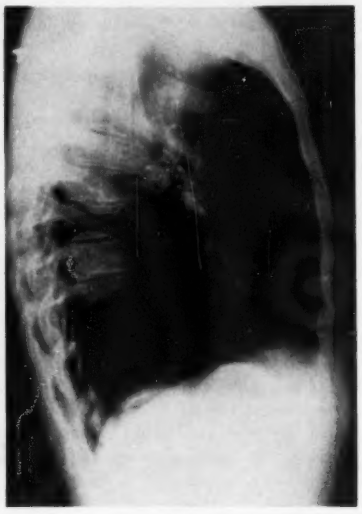

Fig. 1. Chest radiograph, left oblique view, of Patient B. F. (A-30672).

The physical examination revealed a well-developed, well-nourished white man weighing 65 kg. (145 lb.) who was in no acute distress. The skin of his face was rather red in color but without cyanosis. The oral and buccal mucosa were normal in appearance. His temperature was normal, blood pressure 150/80, heart rate 90 per minute. He did not have any clubbing of the fingers nor any cyanosis of the nail beds. The rest of the physical examination was essentially negative. The urinalysis and serology were negative. Hemoglobin level was reported to be 17.0 gm. and the erythrocyte count was 7.5 million. The leukocyte count was 6,600 with a normal differential count. This high level of hemoglobin and erythrocytes led to a recount on the next day. The result was: hemoglobin 18.0 gm., erythrocytes 8.5 million. The hematocrit was 61 per cent and the sedimentation rate was 1 mm. in the first hour. The x-ray of the chest, especially the left oblique view (Fig. 1), revealed a large tumor mass located posteriorly in the region of the ninth and tenth dorsal vertebrae. The radiologist suggested that the possibility of a neuroganglioma must be seriously consideration. Aside from the evidence of calcification at the apex of the right lung the chest x-ray showed no other

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Presented before The Detroit Surgical Association, October 28, 1958.

abnormalities. The old-tuberculin test was three-plus positive and the sputum studies for tubercule bacillus were negative.

*Operation.*—The operation was performed on the third hospital day under semiclosed endotracheal general anesthesia. The left thoracic space was entered through the bed of the partially resected seventh rib. A tumor mass, measuring about 5 cm. in diameter and located posteriorly in the chest and covered completely by parietal pleura, was revealed (Fig. 2). The lung was not involved with this mass. The mass felt somewhat spongy to palpation. There was a rather broad extension from this mass in a lateral and inferior direction to the region of the base of the ninth rib. This direction of the pedicle aroused the suspicion of the mass being a cyst of spinal canal origin. A needle was inserted into the mass and bright blood was aspirated. Palpation of the pedicle revealed a large varicosity. A segment of the ninth rib was carefully resected exposing a dilated vein. This vein measured approximately 5 to 7 mm. in diameter. Upon dissection, the artery which was also markedly dilated, was found to be immediately below this vein. By progressing posteriorly to the angle of the rib, the artery and vein were both dissected and ligated. The pleura was then incised and the vein and artery were pulled inside the chest. The pleura over the mass was also incised and the mass was removed after being carefully dissected from the surrounding tissue. The chest wound was closed after leaving one catheter tube drain. During the surgery, the patient received 2 pints of blood.

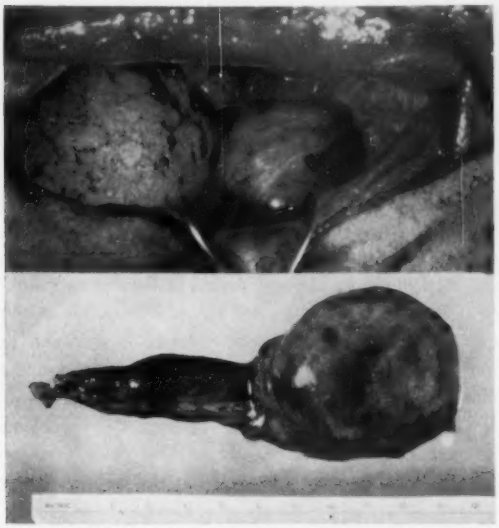

Fig. 2. *(above)* Fistulous mass *in situ* at operating table.
Fig. 3. *(below)* Gross specimen after removal.

The patient's postoperative course was uneventful. The checkup x-ray reported the disappearance of the tumor mass and a postoperative chest without complications. The blood count on the first postoperative day recorded: hemoglobin 14.9 gm.; erythrocytes, 4.9 million; icteric index, 7.0 units; serum bilirubin, 0.7 mg. The second blood count was taken on the fifth postoperative day and showed: hemoglobin 13.6 gm.; erythrocytes 4.6 million; leukocytes 6,200 with a normal differential count.

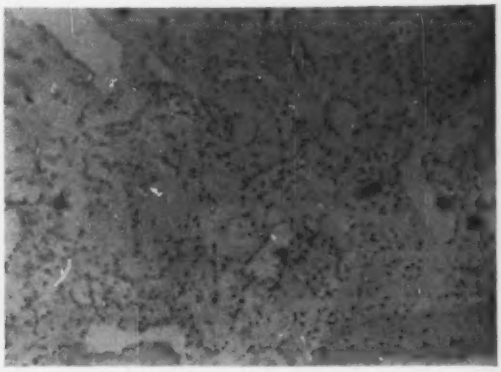

Fig. 4. Microscopic section of mass.

*Pathology.*—The specimen measured 6 x 5 x 5 cm. and was partially encapsulated by membranous tissue. A slender strip of tissue was attached to this mass measuring 5 x 1 x 0.5 cm. and containing a large vein and a narrow artery. Grossly, the vein extended into the mass. The cut sections of the mass were of a fleshy, pale-brown appearance, and the cystic spaces were filled with serosanguinous fluid. The specimen was kept in saline before being photographed (Fig. 3).

Microscopic sections of the mass revealed it to be composed of dilated sinuses which were lined by a single layer of endothelium and many dilated capillaries. The vascular spaces were, in general, surrounded by loose fibro-elastic connective tissue. Some veins showed partial hyalinization of their wall (Fig. 4).

## Discussion

The salient points of this case present a number of interesting features. Though a detailed report on the clinical manifestations, pathogenesis, et cetera, is beyond the scope of this presentation, some conclusions reached through this experience are worth enumerating.

The extreme rarity of such localization of an A-V communication is vouched for by the fact that no other report dealing with another such case could be discovered in the various medical journals. A second point worthy of mention is the comparative difficulty of diagnosis of such cases through the usual clinical methods. The high hemoglobin and erythrocyte counts were the only preoperative findings suggesting the possibility of a congenital A-V communication. As has been suggested above, this lack of clinical symptoms in the patient may be the

*(Continued on Page 101)*

# Hypertension in Infancy and Childhood

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ALTHOUGH significant hypertension is infrequently encountered in infants and children, its presence constitutes an extremely important finding since many forms occurring in the pediatric age-group can be treated successfully. It is the plan of this paper to discuss the measurement of blood pressure in children and to present a systematic approach to the investigation of hypertension with special emphasis on the more frequently encountered conditions. Present-day concepts of therapy will be outlined for each diagnostic possibility.

## Blood Pressure Determination

In determining blood pressure in children, careful attention must be paid to the conditions of the examination, the technique of obtaining the blood pressure, and the interpretation of the results in respect to the normal values for a particular age group. Studies by Clayton and Hughes[4] on hospitalized children revealed that systolic pressure differences of as much as 30 mm. Hg. could occur because of apprehension. No doubt the same could be said for the office situation as well. Such devices as showing the child the equipment, demonstrating the inflation of the cuff, and directing attention to the dial or mercury column may serve to allay apprehension, and allow a rapid accurate determination under more favorable conditions. In small infants, having the mother hold the baby on her lap, or feeding the infant may prove helpful. An isolated finding of hypertension during the physical examination should always be confirmed by repeated determinations. A blood pressure determination should be performed by the second year of life and repeated at the pre-school examination, but earlier determinations should be performed particularly where cardiovascular or renal disease is suspected.

*Technique.*—The auscultatory method using either a mercury or spring sphygomomanometer can be utilized in most examinations. The selection of a proper cuff size is extremely important, as too wide a cuff gives low values, while a narrow cuff falsely elevates the pressure.[26] A properly fitted cuff should cover roughly two-thirds of the upper arm. If various sized cuffs are not available, folding the cuff to adapt it to the smaller extremity is permissible. Again the folded cuff should cover approximately two-thirds of the upper arm. To allow for easier ascultation of the brachial pulse, its position should be located by palpation and the stethoscope bell placed lightly but snugly over this area. The systolic pressure is recorded at the point of appearance of the pulse sounds, and the diastolic pressure recorded at the point of disappearance of the sounds.[1] In determining the leg blood pressure, the same sized cuff as was placed on the arm is used on the thigh, and the stethoscope bell is placed in the popliteal fossa. Normally the systolic pressure in the legs is 10 to 40 mm. Hg. higher than in the arms, while the diastolic pressures are usually equal.

In small infants when blood pressure cannot be determined by the auscultatory method, an approximation of the systolic pressure can usually be made by palpation of the radial pulse as the cuff is deflated or by noting the pressure at which the onset of oscillations occur on the anaeroid dial.

More recently the "Flush" technique has been described[16,24] for use in determining the systolic blood pressure in small infants.

## Determination of Blood Pressure by the "Flush" Technique

A 5 cm. cuff is placed around the ankle or wrist after which an elastic bandage is wrapped snugly around the part, starting distally to express blood from the extremity. The cuff is then inflated to a point higher than the suspected systolic pressure. The elastic bandage is then removed exposing the blanched extremity. Pressure is gradually reduced (6 to 7 mm./second) and the pressure recorded at the point where there is visible flushing of the extremity. Pres-

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sures obtained by this means are lower than those obtained by the auscultatory method and correspond more closely to the mean arterial blood pressure. It should be emphasized that leg blood pressure obtained using the flush technique may be lower than the arm pressure under six months of age. When coarctation of the aorta exists, the differences are striking.

TABLE I. NORMAL BLOOD PRESSURE VALUES FOR INFANTS AND CHILDREN*

| | Systolic | Diastolic |
|---|---|---|
| Newborn | 80 | 45 |
| ½ to 5 years | 90±25 | 55±15 |
| 6 to 10 years | 100-110±15 | 60±10 |
| 11 to 15 years | 110-126±15 | 60±10 |

*Adapted from Smith, C.A.[27], Haggerty, R. J., et al[19], and Graham, A. W., et al[17].

## Normal Blood Pressure Values in Infants and Children

In the newborn infant, the upper limit of normal blood pressure is in the range of 80 mm. Hg. systolic pressure, with a diastolic pressure of 45 mm. Hg.[27] Blood pressure values for infancy and childhood are presented in Table I. In general, a blood pressure recorded under basal conditions at 15 to 20 mm. Hg. over the accepted norm is significant. It is well to repeat the determination on subsequent visits should this be an isolated finding. If significant elevation persists, then one should proceed with the various diagnostic possibilities. In hospitalized children, the cuff may be left on and blood pressure determinations obtained during sleep.

## Etiology of Hypertension

The more common causes of hypertension in infancy and childhood will be discussed as individual entities. Table II lists the important diagnostic[12] studies utilized in the evaluation of hypertension. Table III summarizes the commonly encountered conditions, their diagnostic features, and suggested therapy. Of the entities to be discussed, renal disease is by far the most common cause of hypertension occurring in childhood.

### I. *Renal*

(A) *Acute Hemorrhagic Nephritis.*—Acute hemorrhagic nephritis has a high incidence (50 to 60 per cent) of associated hypertension.[22] Although the hypertension is of short duration (average eight days), the concurrent complications, hypertensive encephalopathy and cardiac failure, account for the majority of deaths observed during the acute phase. Since both of these complications are preceded by a rising blood pressure, the physician can anticipate and avoid their occurrence in the majority of subjects by serial measurements of the child's blood pressure during the first week or two of the disease and observing for signs and symptoms of encephalopathy (irritability, headache, progressing to coma and convulsions) or of cardiac failure (restlessness, increasing heart size, rising pulse rate, and basilar rales).

TABLE II. EXAMINATIONS USED IN EVALUATION OF HYPERTENSIVE DISEASE IN CHILDHOOD**

* 1. Palpation of femoral pulses and measurement of blood pressure in all four extremities.
* 2. Examination of ocular fundi.
* 3. Urinalysis.
* 4. X-ray examination of the thorax.
* 5. Determination of blood urea nitrogen.
6. Electrocardiographic examination.
7. Determination of serum potassium, sodium, calcium, bicarbonate and chloride.
8. Excretory urography.
9. Retrograde pyelography with "split" function tests.
10. Radioactive diodrast clearance test.
11. Regitine test.
Determination of urinary catecholamines.
12. Renal arteriography.
13. Determination of urinary excretion of lead and mercury.
14. Determination of urinary pattern of steroid excretion.

* Routine
** Modified after Fairbairn, J. F., II.[12]

On occasion, the physician may be consulted regarding a child with manifest encephalopathy or cardiac failure while the antecedent signs and symptoms of nephritis may have been overlooked or obscured by the severity of the complicating encephalopathy or heart failure. Inclusion of acute nephritis in the differential diagnosis of hypertension in children in whom a rapid development of a comatous state or heart failure has occurred, will avoid needless delay in proper diagnosis and therapy.

*Management.*—In the majority of children, complications associated with the hypertension of acute nephritis do not occur until the blood pressure rises over 140/90. Hypertension beneath these levels unless accompanied by symptoms usually requires no therapy. However, sudden crises in which the blood pressure rapidly rises may occur. Thus, repeated observation of the blood pressure should be made within the first week or ten days of the disease.

In recent years, newer hypotensive agents have become available which induce a rapid and effective drop in the hypertension of acute nephritis and which, in the recommended dosage, cause neither significant impairment in renal function nor drop of blood pressure to hypotensive levels. For the past two years, we have used the following program (essentially in

the manner recommended by Etteldorf[11] and Daeschner[7]) and have obtained gratifying results (Table IV).

For hypertension (140/90 or higher) reserpine (purified alkaloid of Rauwolfa serpentina) 0.10 mg./kg. of weight intramuscularly is given as a single dose. The onset of response occurs between one-half and two hours after administration and continues for eleven to eighteen hours. In many subjects hypertension does not recur. For those patients in whom hypertension returns, the above dosage is repeated as need arises, until hypertension ceases. It should be noted that oral reserpine may not be effective until seven to fourteen days after onset of therapy, thus is of no value in the treatment of acute hypertension, regardless of cause.

In a small percentage of children, a significant response does not occur on the above program. If after three to six hours of serial blood pressure observa-

TABLE III. HYPERTENSION IN CHILDHOOD
Diagnostic Aids Useful in Determining the Etiology and Specific Therapy Indicated

| Disease | Diagnostic Points | Therapy |
|---|---|---|
| 1. Acute hemorrhagic nephritis | Clinical picture—<br>Urinalyses<br>Blood urea nitrogen<br>Urea clearances<br>ASO titer | Parenteral reserpine and Apresoline®, or magnesium sulfate |
| 2. Chronic nephritis | Growth failure<br>Refractory anemia<br>Urinalyses<br>Concentration tests<br>Urea clearances<br>Renal biopsy | Oral reserpine and chlorothiazide; other anti-hypertensive agents |
| 3. Obstructive lesions of the renal arteries | Radioactive diodrast clearance<br>Aortogram<br>Intravenous pyelograms | Resection of stenotic artery |
| 4. Renal vascular insufficiency associated with renal hypoplasia or chronic pyelonephritis | Recurrent pyelonephritis<br>Urinalyses with cultures<br>Intravenous pyelograms<br>Retrograde pyelograms<br>"Split" renal functions<br>Radioactive diodrast clearance<br>Aortogram | Surgical correction of obstructive lesions; nephrectomy if disease completely confined to one kidney |
| 5. Renal neoplasms | Mass in flank<br>Intravenous pyelograms<br>Retrograde pyelograms | Nephrectomy; postoperative irradiation |
| 6. Coarctation of the aorta | Femoral pulses<br>Determination of blood pressure in all four extremities | Resection of stenotic area |
| 7. Patent ductus arteriosus | Frequent bouts of pneumonia<br>Machinery-like murmur at left base | Surgical closure |
| 8. Pheochromocytoma | Regitine test<br>Urinary catechol amine test<br>Intravenous pyelograms | Surgical excision |
| 9. Cushing's syndrome | Clinical picture<br>History of steroid therapy | Surgical excision; discontinue or decrease dosage of steroids |
| 10. Congenital adrenal hyperplasia | Pseudohermaphrodism<br>In males, masculinization<br>Urinary steroid excretion pattern | Steroid therapy |
| 11. Hyperthyroidism | Clinical picture<br>PBI<br>$I^{131}$ uptake | Anti-thyroid medication; subtotal thyroidectomy |
| 12. Central nervous system disease | Clinical picture<br>Lumbar puncture<br>Skull x-rays<br>Ventriculogram | Supportive excision of tumor |
| 13. Familial dysautonomia | Family history<br>Clinical picture | Supportive sedation |
| 14. Mercury poisoning | Clinical picture<br>Urinary mercury excretion | (?) Steroid therapy |
| 15. Lead poisoning | Clinical picture<br>Anemia, stippled cells<br>X-rays of long bones<br>Urine coproporphyrin<br>Urine lead excretion | Calcium ethylene diamine-tetra-acetic acid |
| 16. Essential hypertension | Family history<br>? cold pressor and amobarbital tests | Phenobarbital; anti-hypertensive agents |

TABLE IV. ANTI-HYPERTENSIVE AGENTS USEFUL IN PEDIATRICS

| Drug | Site of Action | Parenteral Dose | Oral Dose | Side Effects |
|---|---|---|---|---|
| Rauwolfia serpentina (reserpine) | Central | 0.10 mg./kg. I.M. and q. 8-12 hr. | 0.12-0.50 mg. b.i.d. q.d. (0.02-0.03 mg./kg./24 hr.) | Drowsiness, nasal congestion, brady cardia, depression |
| Hydralazine hydrochloride (Apresoline®) | Central | 0.10 mg./kg. I.M. q. 8-12 hr. (preferably in combination with reserpine) | 10-25 mg. t.i.d. or q.i.d. | Early: Headache, palpitation, tachycardia, vomiting<br>Delayed: Lupus erythematosus with rheumatoid arthritis, severe depression |
| Magnesium sulfate | ? arteriolar smooth muscle | 150-200 mg./kg. (5-7 cc. of a 3% solution/kg.) I.V. in one hour. 0.2-0.4 cc./kg. of 25% solution I.M. q. 4-6 hour. | | Infrequent but manifest by respiratory depression; responds specifically to calcium gluconate |
| Mecamylamine hydrochloride (Inversine®) | Ganglionic blocking agent | | 1-6 mg. b.i.d. | Orthostatic, hypotension, constipation, paralytic ileus |
| Chlorothiazide (Diuril®) | ? renal tubule arteriolar smooth muscle | | 30-50 mg. per kg./24 hr. | Hypokalemia |

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tions, a reduction of blood pressure below 140/90 has not occurred, hydralazine hydrochloride by intramuscular injection will produce additive hypotensive effect. The recommended dosage is 0.10 mg./kg. The combined hypotensive effects continue for twelve to twenty-four hours. Thereafter, repetition of administration of the two above-mentioned drugs intramuscularly in the above dosages but given simultaneously may be continued as dictated by the course of the hypertension. In the presence of convulsions or heart failure, the combination may be used at the onset to treat the hypertension. Often, only one such injection will be required.

A time-honored and reliable agent, magnesium sulfate, has been widely used for the hypertension associated with acute nephritis. For intramuscular injection, a concentration of 25 per cent is utilized, administering 0.2 to 0.4 cc./kg. of weight. The drug is effective in one to two hours but frequently repeated doses will be required to maintain a satisfactory level of blood pressure. The use of magnesium sulfate has not been outmoded by the newer antihypertensive agents, but the need for frequent injections (four to eight hour intervals) of relatively large volumes (4 to 8 cc.) with the attendant pain at the injection site constitutes a distinct disadvantage.

It is to be emphasized that both the need for antihypertensive drug therapy in acute nephritis and the response to therapy are determined by serial blood pressure measurements. The program of therapy should be individualized for each child since the severity and duration of the hypertension is extremely variable.

(B) *Chronic Nephritis.*—In children, as in adults, chronic nephritis may be complicated by hypertension. The presence of a chronic renal disease may be suggested by certain symptoms: growth failure, refractory anemia, recurrent bouts of vomiting or dehydration, or both, without apparent cause. At times, however, the first symptoms may be identical to, and as precipitous in onset, as those encountered in acute nephritis. Separation of the two entities, thus, may not be made in certain children during the initial hospitalization. In such instances, long-term observation will be required to determine the ultimate diagnosis and prognosis.

It should be recalled that a chronic form of nephritis has been observed in childhood following anaphylactoid (Schonlein-Henoch syndrome) purpura, intensive irradiation to the abdomen, or associated with disseminated lupus erythematosis, progressive lipodystrophy, and polyarteritis. In general, the nephritis observed in these situations is progressive with a more rapid course than in the usual form of chronic nephritis.

Despite the persistence of renal disease as manifest by urinary abnormalities, the course of the hypertension in chronic nephritis may be quite variable. It may be severe during an exacerbation of the nephritis, then disappear several weeks or months later only to recur with subsequent flare-ups of the renal disease. On occasion in children, persistent hypertension requiring constant anti-hypertensive therapy may be encountered.

*Management.*—During an acute phase of hypertension when pressures are 140/90 or above, the program of therapy which we have employed has included as initial drugs, reserpine and chlorothiazide. Despite its marked antihypertensive effects in acute nephritis, magnesium sulfate is without effect in

chronic nephritis. However, this difference in response may be useful diagnostically at times in distinguishing between the two conditions.

1. The reserpine is administered parenterally using the dosage and schedule as outlined for acute nephritis.

2. Chlorothiazide has proved to be an effective hypotensive agent when administered alone to hypertensive patients,[14] but has in general been utilized to augment the effect of other anti-hypertensive drugs. The drug has been as effective in children as in adults, and is administered orally in divided doses in the total amount of 30 to 50 mg./kg./day.[5] Since chlorothiazide is thought to exert its major pharmacologic effect on hypertension through its action on renal transport of electrolytes, a reasonably good urinary flow should be present in the subject or the hypotensive response may not be depended upon. The major adverse effect of chlorothiazide has been a decrease of serum electrolytes, particularly potassium. In children on general diets, we have not encountered significant hypokalemia during long-term (six to twelve months) therapy but have observed its occurrence in subjects on low salt diets. For subjects on low sodium diets or those in whom hypokalemia develops, supplements of potassium chloride 2.0 gm. per day may be administered.

If the combination of reserpine (parenterally) and chlorothiazide (orally) do not lower the blood pressure satisfactorily, hydralazine may be added again utilizing the dosage outlined under the therapy of hypertension in acute nephritis.[11]

On a rare occasion, when the combination of reserpine, chlorothiazide, and hydralazine are unsuccessful in maintaining satisfactory reduction in blood pressure, a ganglionic blocking agent such as mecamylamine (Table IV) may be substituted for the hydralazine.

For long-term control of hypertension, oral therapy is preferred. The combination of reserpine and chlorothiazide has given good results in the majority of subjects under our care who have required long-term management. The chlorothiazide is administered, as discussed previously, in a dosage of 30 to 50 mg./kg./day. Reserpine is begun with a dosage of 0.12 mg. b.i.d. until control of hypertension is effected or signs of toxicity (severe nasal stuffiness, excessive drowsiness, depressive tendency) develop. As a general rule, we have not attempted to lower the blood pressure of these subjects to normal levels but have aimed at maintaining a range fairly close to 130-140/80-90. In individuals with renal disease and hypertension, a normal blood pressure may be incompatible with adequate renal blood flow, thereby impairing renal function.

In instances of failure to effect long-term control of hypertension or during exacerbations of severe hypertension, we have recommended hospitalization for optimal observations of the patient during additions of hydralazine or ganglionic blocking agents.

(C) *Obstructive Lesions of the Renal Arteries.*—Any lesion that can give rise to a significant degree of renal arterial stenosis may result in hypertension. In children this will include a variety of congenital lesions among which are stenosis of the renal artery, aneurysms and other aortic anomalies occluding the renal artery, and multiple renal arteries with stenosis or occlusion of one or more branches.[8] This group, while probably small, is very important since specific therapy is possible. The following case summary will illustrate this point.

### Illustrative Case

The patient, a five-year-old girl, was seen for her pre-school physical examination and found to have a blood pressure of 186/140 which persisted upon repeat examinations. She was asymptomatic. The physical examination (including evaluation of her eye grounds) was entirely within normal limits except for the presence of significant hypertension. Urinalysis and renal function studies were normal. The intravenous pyelograms were also interpreted as normal. The administration of Regitine® did not produce a fall in blood pressure. A retrograde aortogram was performed by inserting a side-hold catheter into the aorta through the femoral artery and injecting 85 per cent Hypaque.® This study demonstrated stenosis of the right renal artery. Resection of the stenotic area and an end-to-end anastomosis resulted in a prompt fall in blood pressure to normal limits (110-120/70) where these levels have persisted.

*Comment:* It is important to stress that this child was entirely asymptomatic except for the finding of significant hypertension on the pre-school physical examination. Although the routine diagnostic studies (including intravenous pyelograms) were normal, aortography demonstrated the lesion which was removed by resection.

A cure of the hypertension resulted.

(D) *Renal Vascular Insufficiency Associated with Renal Hypoplasia and/or Chronic Pyelonephritis.*—Recently, Welch and his associates,[28] have reported a series of fifteen children with hypertension associated with pyelonephritis or renal hypoplasia who were treated by nephrectomy. Of eleven patients with unilateral disease so treated, long-term observations

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(two-and-one-half to eleven years) indicated an excellent response in eight patients. (Of four subjects, however, with bilateral renal disease but more severe in one kidney, removal of the predominantly diseased kidney resulted in a poor response in all four). This report focuses attention upon a recognizable and potentially remedial cause of hypertension in children in which a parenchymatous (congenital or acquired) renal defect appears to be associated with renal ischemia.

The symptomatology of children with this variety of hypertension may relate either to the hypertension, with resultant headaches, convulsions or cardiovascular symptoms, or focus attention to the urinary tract. The latter event is more common and in such cases, most frequently, signs of recurrent or persistent infection of the urinary tract are found. Regardless of the presence or absence of symptoms suggesting urinary tract infection, the possibility of a unilateral hypoplastic or degenerative renal lesion should be considered in all children found to have hypertension. Evaluation should include excretory urography as one of the initial steps in diagnosis. Demonstration of absent or poor function in one kidney, or a definable obstructive lesion is an indication for further determining the affected kidney's functional capacity. Frequently, valuable information may be obtained by so-called "split function" studies utilizing simultaneous bilateral ureteral catheterizations. At times (particularly in young children) such a procedure may be difficult to perform or unreliable in interpretation. An indirect method of obtaining similar data has been recently reported in which a small quantity of radioactive diodrast is injected intravenously and the rate and ultimate concentration of the material accumulated by each kidney is detected with a sensitive scintillation counter.[30] If the above investigations fail to indicate clearly the type and magnitude of the renal defect, aortography may afford an estimate of the comparative vascularity of the two kidneys, and contribute data essential in the decision regarding nephrectomy. Again, it should be emphasized that if both kidneys are found to be abnormal, although one kidney is clearly more abnormal than the other, removal of the more diseased organ may not result in a cure of hypertension.

### Illustrative Case

We have recently observed this course in a three-year-old girl presenting with severe hypertension (260/180). Studies, including aortogram, demonstrated poor function and poor vascularity of the right kidney. The arterial supply to the left kidney was abnormal (three small arteries, no main trunk) but blood flow appeared good. Elective right nephrectomy produced a significant drop in blood pressure but never to normal, and evidences of disease in the left kidney were persistently demonstrated (albuminuria, slightly elevated blood urea nitrogen). Following a period of one year during which time blood pressure was maintained at 150/100 (using continuous drug therapy), a sudden rise of blood pressure occurred which did not respond to numerous hypotensive agents. A surgical attempt (splenorenal arterial shunt) to improve blood supply to the remaining left kidney was unsuccessful and the patient succumbed to congestive heart failure several days following the surgical procedure.

(E) *Renal Neoplasms.*—The presenting symptoms of a child with an embryoma of the kidney (Wilm's Tumor) is most commonly the finding by the mother or physician of a painless swelling in the abdomen. Urinary complaints are rare but hematuria is occasionally observed. In a small percentage (approximately 10 per cent) hypertension is detected. The occurrence of hypertension is significant primarily in affording confusion in differential diagnosis. Although the firm feel of a solid tumor is quite distinct from that noted in a cystic collection of fluid (massive hydronephrosis for example) at times the hydronephrotic sac may be under sufficient tension to give the examiner the impression that he is palpating a solid mass. Thus, the presence or absence of hypertension does not differentiate between the cause for the mass. If prompt investigation (including intravenous pyelography and perhaps retrograde pyelography to rule out hydronephrosis) demonstrate that a renal tumor is indeed present, it is, of course, an indication for immediate removal followed by postoperative irradiation as outlined by Gross.[18]

(F) *Post-irradiation Nephritis.*—The occurrence of a clinical picture of chronic nephritis with hypertension following irradiation to the abdomen has been observed in children treated for abdominal neoplasms. Fortunately, it is not a common sequella. The nephritis may develop a few months following irradiation[31] or several years later.[21] The disease may show a rapid termination to uremia, or may follow a more leisurely progression. The following case is considered an example of post-irradiation nephritis, although a biopsy to confirm the diagnosis was not obtained.

### Illustrative Case

A boy, aged fourteen, was seen by his family physician for a routine pre-school examination on August 18, 1958. On that occasion, hypertension, hematuria, and albuminuria were found. He then was referred to the University Hospital for further evaluation. Past history revealed that the

patient had had a right nephrectomy at the age of three-and-one-half years. Pathologically, the right kidney parenchyma was replaced by a tumor mass with characteristics typical of a Wilm's tumor.

The patient received irradiation therapy preoperatively and postoperatively with a total dosage of 1675 Roentgens to the right anterior abdomen and 1650 Roentgens to the right posterior abdomen. Over the past three months the patient had had frequent headaches accompanied by ease of fatigue.

Physical examination on admission on August 25, 1958, revealed a boy not appearing ill. Blood pressure was 180/110, pulse rate was 80 per minute and respiratory rate was 20 per minute. Minimal papilledema was present bilaterally with some tortuosity and AV nicking of the blood vessels. Urinalysis showed 2+ to 3+ albuminuria and microscopic hematuria. A twenty-four-hour urea clearance was normal and the excretory pyelogram showed a normal, but hypertrophied, kidney on the left. A Regitine test was negative.

The patient was discharged on a daily dose of reserpine 0.25 mg. q.i.d. orally, and his blood pressure has decreased subsequently to approximately 140/80. He is symptom-free, but albuminuria and hematuria persist.

## II. *Cardiovascular*

(A) *Coarctation of the Aorta.*—Routine palpation of the femoral pulses constitutes an extremely important part of the pediatric physical examination. Inability to palpate the femoral pulse, diminished femoral pulsations, or a pulse lag in the lower extremity, should be followed by blood pressure determinations in the arms and legs. The presence of hypertension in the arms and relative hypotension in the legs is diagnostic of coarctation of the aorta. It is worthwhile to compare readings in the upper extremities since the left arm reading will be significantly lower if the left subclavian artery is at or below the site of coarctation. Concerning surgical management, we have felt that repair should be undertaken between ages eight and twelve years. However, in the infant who presents with congestive heart failure and cannot be maintained on a medical program, earlier operation must be performed.

(B) *Patent Ductus Arteriosus.*—Bounding peripheral pulses, a widened pulse pressure in association with a machinery-like murmur (heard best at the left base) should diagnose the presence of a patent ductus arteriosus. Similar findings with the murmur localized somewhat lower along the left sternal border would suggest the possibility of an aorticopulmonary fenestration. Hypertension may occur in the postoperative period following repair of a patent ductus arteriosus probably due to a sudden increase in the systemic blood volume. This is usually transient and requires no specific therapy except to limit intravenous fluids over the immediate postoperative period. In regard to the time for surgical correction, we have recommended surgical repair as soon as the diagnosis is established regardless of age as long as a flow from the aorta to the pulmonary artery exists. Recent evidence would suggest that if these children are to realize their full growth potential, repair should take place prior to age three years, particularly in symptomatic patients.[10]

## III. *Endocrine*

(A) *Disorders of the Adrenal Gland.*—

(1) *Pheochromocytoma.*—Daeschner[6] has reviewed sixteen published reports of this tumor occurring in children under the age of fourteen years. Since this entity represents a curable type of hypertension, considerable effort should be made to establish the diagnosis. In children the hypertension is more likely to be persistent rather than occurring in paroxysmal episodes as had been described in adults. The Regitine test[15] when positive as evidenced by a significant drop in blood pressure following its intravenous administration is highly suggestive of the presence of a chromaffin tumor. False positive and negative results have been reported. Therefore, this test may only be considered a screening device. At present, the determination of the urinary catechol amines which are markedly elevated in the presence of a pheochromocytoma is the diagnostic procedure of choice. An intravenous pyelogram may aid in abdominal localization. It is well to point out that these tumors may be extra-adrenal, bilateral, and can occur in the thorax.

(2) *Cushing's Syndrome.*—Adrenal tumor or hyperplasia may produce the characteristic clinical picture of buffalo-type obesity, moon facies, striae, acneiform eruption and hirsutism. Hypertension occurred in approximately 90 per cent of the reported cases.[29] More commonly, Cushing's syndrome may appear secondary to the use of steroid therapy. No steroid preparation in current use has been free of this side-effect.

(3) *Congenital Adrenal Hyperplasia.*—Eberlein and Bongiovani have described a seven-and-one-half-year-old female pseudohermaphrodite who had associated hypertension.[9] The steroid excretion pattern in the urine differed from the usual pattern seen with the adrenogenital syndrome suggesting another enzymatic

defect in steroid biosynthesis. On cortisone therapy, the blood pressure fell to normal limits.

(B) *Thyroid Disorders.*—In a review of a large series of children with hyperthyroidism, Kennedy has reported almost constant elevation of the systolic pressure and pulse pressure.[20] Attention is usually directed to the presence of thyroid enlargement, eye changes, weight loss (despite increased appetite), weakness, irritability, and thermal sensitivity. Hypertension will subside on a program utilizing anti-thyroid medication or following thyroidectomy.

### IV. *Central Nervous System*

(A) *The presence of hypertension in association with brain tumors,* according to Ford,[13] is rare. Hypertension has been noted with inflammatory disease and cerebral hemorrhage secondary to trauma. In poliomyelitis, elevation of the blood pressure may occur during the acute stage in association with the bulbar form, or during the convalescent stages the explanation of which not being completely understood. In all instances where hypertension occurs with disorders of central nervous system, the neurologic findings predominate, with elevation of the blood pressure a secondary finding.

(B) *Familial Dysautonomia.*—This condition is manifested by specific disorders of autonomic function including diminished lacrimation, hyperhydrosis, transient skin blotching, abnormal swallowing reflex, behaviorial disorders, and faulty temperature control. Almost all cases described have occurred in Jewish children. Many patients exhibit a labile blood pressure with swings from hypertension to postural hypotension.[25]

### V. *Poisonings*

Of the many substances which children ingest, mercury and lead are the only significant agents producing severe persistent hypertension in the pediatric age group.

(A) *Mercury.*—The classic picture of mercury poisoning has been termed acrodynia and in the typical case is manifest by extreme irritability, listlessness, photophobia, erythematous, wet, cold fingers and toes. Hypertension is frequent and severe. Of seven patients all under four years of age with acrodynia, observed at the University Hospital over a six-year period (1948-1954), two had severe hypertension (180-210/120) and three had moderate hypertension (125-140/90). The diagnosis is made by recognition of the clinical picture and confirmed by the detection of abnormal quantities of mercury in the urine. Therapy with steroids and supplementary sodium chloride has been recommended.[2,3]

(B) *Lead.*—Hypertension in lead poisoning occurs in conjunction with other manifestations of the clinical and laboratory picture: encephalopathy, anemia with stippled erythrocytes, radiographic changes in the long bones, glycosuria and aminoaciduria. A history of exposure may be helpful in supporting this diagnosis. A clinical suspicion of lead poisoning should establish the need for careful review of the history. Laboratory studies should include a determination of the lead excreted in the urine. Calcium ethylenediamine tetraacetic acid (EDTA) has been proven clinically effective in the therapy of children with lead poisoning. During the phase of encephalopathy with marked cerebral edema, surgical decompression of the brain has been recommended as an aid in the prevention of further cerebral damage.[22]

### VI. *Essential Hypertension*

Haggerty and his co-workers,[19] reviewed a series of nine patients thought to have essential hypertension. Only ten other authenticated cases have been reported, testifying to the rarity of this entity in children. Five of the patients had severe hypertension with secondary retinal and renal changes, while in the other four, blood pressure recordings were never over 160/110. In the latter group, a positive family history of hypertension was obtained. The diagnosis must be established on the basis of exclusion of other causes of hypertension, because no definitive test is available at present.

## Summary

Hypertension may be as damaging to the child as to the adult. The routine pediatric examination should include determination of the blood pressure. This is particularly pertinent inasmuch as many of the causes of hypertension in children can be completely corrected by appropriate therapy.

Establishment of the presence of significant hypertension in a child requires consideration of the technique utilized in measurement, the emotional state of the child at the time of blood pressure determination, and the normal range of blood pressure for a particular age group.

The more frequent causes of hypertension in childhood have been discussed. The salient features of

diagnosis and current methods of management have been emphasized.

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## References

1. Bordley, J., III, Conner, C. A. R., Hamilton, W. F., Kerr, W. J., and Wiggers, C. J.: Recommendations for human blood pressure determinations by sphygomomanometers. Circulation, 4:503-509, 1951.

2. Cheek, D. B., Bondy, R. K., and Johnson, L. R.: The effect of mercurous chloride (Calomel) and epinephrine (sympathetic stimulation) on rats. Pediatrics, 23:302-313, 1959.

3. Cheek, D. B., and Hicks, C. S.: Pink disease or infantile acrodynia: Its nature, prevention and cure. M. J. Australia, 1:107, 1950.

4. Clayton, G. W., Jr., and Hughes, J. G.: Variations in blood pressure in hospitalized children. J. Pediat., 40:462-468, 1952.

5. Crawford, J. D.: Chlorothiazide. Pediatrics, 22:236-237, 1958.

6. Daeschner, C. W., Moyer, J. H., and Able, L. W.: Pheochromocytoma in a four-year-old child; renal hemodynamic, pharmacologic and radiographic studies. J. Pediat., 44:141-152, 1954.

7. Daeschner, C. W., Moyer, J. H., Bell, W. R., and Clark, J. L.: Parenteral administration of reserpine in the treatment of hypertension due to acute and chronic nephritis; clinical and renal hemodynamic studies. Pediatrics 19:566-579, 1957.

8. DeChamp, P. T., and Birchall, R.: Recognition and treatment of renal arterial stenosis associated with hypertension. Surgery, 43:134-152, 1958.

9. Eberlein, W. R., and Bongiovanni, A. M.: Congenital adrenal hyperplasia with hypertension: Unusual steroid pattern in blood and urine. J. Clin. Endocrinol., 15:1531-1534, 1955.

10. Engle, M. A., Holswade, G. R., Goldberg, H. P., and Glenn, F.: Present problems pertaining to patency of the ductus arteriosus. I. Persistence of growth retardation after successful surgery. Pediatrics, 21:70-80, 1958.

11. Etteldorf, J. N., Smith, J. D., and Johnson, C.: The effect of reserpine and its combination with hydralazine on blood pressure and renal hemodynamics during the hypertensive phase of acute nephritis in children. J. Pediat., 48:129-139, 1956.

12. Fairbairn, J. F., II: Selection of hypertensive patients for drug treatment. Proc. Staff Meet. Mayo Clin., 33:307-312, 1958.

13. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence. 3rd ed. Springfield, Ill.: Charles C Thomas.

14. Freis, E. D., Wanko, A., Wilson, I. M., and Parrish, A. E.: Treatment of essential hypertension with chlorothiazide (Diuril); Its use alone and combined with other antihypertensive agents. J.A.M.A., 166:137-140, 1958.

15. Gifford, R. W., Jr., Roth, G. M., and Kvale, W. F.: Evaluation of a new adrenolytic drug (Regitine) as a test for pheochromocytoma. J.A.M.A., 149:1628-1634, 1952.

16. Goldring, D., and Wohltmann, H.: Flush method for blood pressure determinations in newborn infants. J. Pediat., 40:285-289, 1952.

17. Graham, A. W., Hines, E. A., Jr., and Gage, R. P.: Blood pressures in children between the ages of five and sixteen years. Am. J. Dis. Child., 69:203-207, 1945.

18. Gross, R. E.: The Surgery of Infancy and Childhood: Its Principles and Techniques. Philadelphia: W. B. Saunders Company, 1953.

19. Haggerty, R. J., Maroney, M. W., and Nadas, A. S.: Essential hypertension in infancy and childhood; differential diagnosis and therapy. Am. J. Dis. Child., 92:535-549, 1956.

20. Kennedy, R. L. J., and Hayles, A. B.: The Thyroid Gland. *In* McQuarrie, I., and Kelley, V. C., eds.: Brennemann's Practice of Pediatrics. Vol. 1, chapter 38. Hagerstown, Md.; W. F. Prior Co., Inc., 1959.

21. Levitt, W. M.: Radiation nephritis. Brit. J. Urol., 29:381-382, 1957.

22. McCrory, W. W., and Nash, F. W.: Hypertension in children: A review. Am. J. M. Sc., 223:671-680, 1952.

23. McLaurin, R. L., and Nichols, J. B., Jr.: Extensive cranial decompression in the treatment of severe lead encephalopathy. Pediatrics, 20:653-667, 1957.

24. Moss, A. J., Liebling, W., Austin, W. O., and Adams, F. H.: An evaluation of the flush method for determining blood pressures in infants. Pediatrics, 20:53-62, 1957.

25. Riley, C. M., Freedman, A. M., and Langford, W. S.: Further observations on familial dysautonomia. Pediatrics, 14:475-480, 1954.

26. Robinow, M., Hamilton, W. F., Woodbury, R. A., and Volpitto, P. R.: Accuracy of clinical determinations of blood pressure in children. Am. J. Dis. Child., 58:102-118, 1939.

27. Smith, C. A.: The Physiology of the Newborn Infant. 2nd ed. Springfield, Ill.: Charles C Thomas, 1951.

28. Welch, H. C., Harris, L. E., and DeWeerd, J. H.: Nephrectomy in juvenile hypertension associated with renal disease: Report of 15 cases. Pediatrics, 21:941-949, 1958.

29. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. 2nd ed. Springfield, Ill.: Charles C Thomas, 1957.

30. Winter, C. C.: A clinical study of new renal function test: The radioactive diodrast renogram. J. Urol., 76:182-196, 1956.

31. Zuelzer, W. W., Palmer, H. D., and Newton, W. A., Jr.: Unusual glomerulonephritis in young children; probably radiation nephritis; report of three cases. Am. J. Path., 26:1019-1039, 1950.

# The Pituitary Gland in the Production of Atherosclerosis

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IT IS the purpose of this article to present experimental data pointing to the role of the pituitary in the production of atherosclerosis. Aschoff[1a] stated that Marchand coined the expression "atherosclerosis" to indicate "the peculiar changes observed, especially in elderly individuals, in the intima of the aorta and large vessels of the elastic type, which are so characteristic of the clinical picture generally termed atherosclerosis. We are indebted to Virchow for the first accurate histological description of the entire process."

Aschoff[1b] stated that Virchow's conception of atherosclerosis was:

The entire atheromatous process represents a primary loosening of the intimal layer, due to infiltration of blood plasma, which is accompanied or followed by a growth of intimal cells and a more marked vascularization of the media. Thus it is an active process in which a fatty metamorphosis of the different layers may take place as well in an entirely passive manner.

The *primum movens* of the entire irritative process is therefore a loosening of the internal coat.

Aschoff's summary of atherosclerosis[1c] in his Lane Lecture at Leland Stanford University bears repeating.

In the atherosclerotic process of the vessels there is a peculiar process of wear and tear of a molecular nature, which we cannot at present understand, but which through subsequent swelling and precipitation processes, especially of lipoid substances and secondary transformation to calcium compounds, acquires a characteristic stamp. It involves a definite specific disease of the supporting substance which occurs not only in the vessel wall, but in other parts of the body as well. Thus the calcium infarct of the kidney papillae, really a fat calcium infarct, is a typical atheromatosis of the kidney supporting substance, which undoubtedly depends on a wear and tear and imbibition process from the continuous tumescence and detumescence of the underlying kidney papillae. To the atheromatous changes belong the so-called senile degeneration of cartilage and the arcus senilis of the eye. As we consider the atheromatosis of the vessels in the light of the larger category of the general processes of wear and tear of the supporting substances, it loses its special qualities which have given rise to so many erroneous theories of infection, et cetera. If that process of wear and tear impresses us most strikingly in the vessel wall, it is due to the fact that our vascular system is the organ which is mechanically under greatest strain.

## Experimental Data

In experimental work begun in 1929 and published in 1930,[14,15] it was reported that posterior lobe extract injected into rabbits being fed a high cholesterol diet produced extensive atheromatous changes much greater in intensity than either a high cholesterol diet or posterior lobe extract. I would like to review the changes found in four groups of rabbits which were divided as follows:

*Control Group.*—Five normal rabbits on a normal laboratory diet.

*Group A.*—Five rabbits on a normal laboratory diet plus the addition of 12 cc. cotton seed oil and 4 gm. of anhydrous lanolin for each rabbit.

*Group B.*—This group consisted of ten rabbits which were placed on the same high fat diet as Group A and in addition received 1 cc. of obstetrical posterior lobe extract (Parke Davis and Company's Commercial Obstetrical Pituitrin) injected either subcutaneously or intraperitoneally.

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The experimental work was carried out in conjunction with Dr. Eugene A. Osius.

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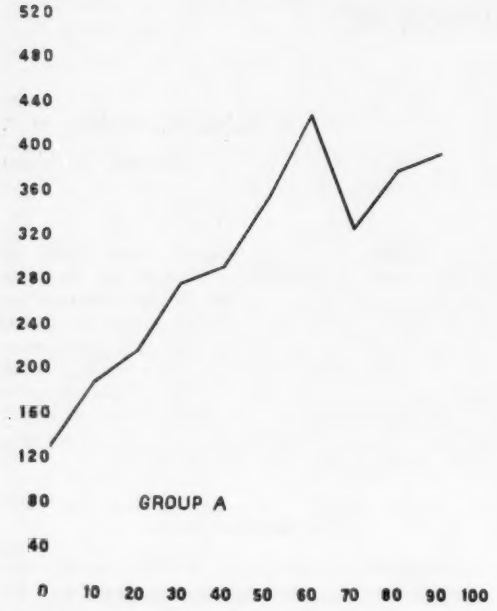



Fig. 1. Group A—On a high cholesterol diet showing rise of cholesterol to 440 mgms. The horizontal lines represent days, the vertical lines, cholesterol in mg.

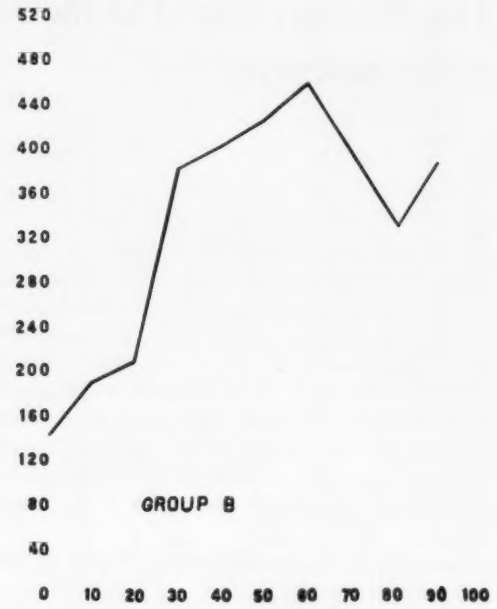



Fig. 2. Group B—On a high cholesterol diet plus posterior lobe extract showing rapid rise of cholesterol to 480 mg.

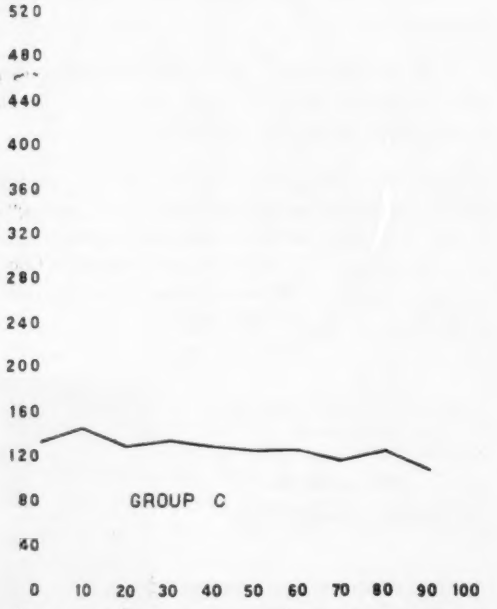



Fig. 3. Group C—On a normal diet plus posterior lobe extract—practically a normal curve—same as control group.

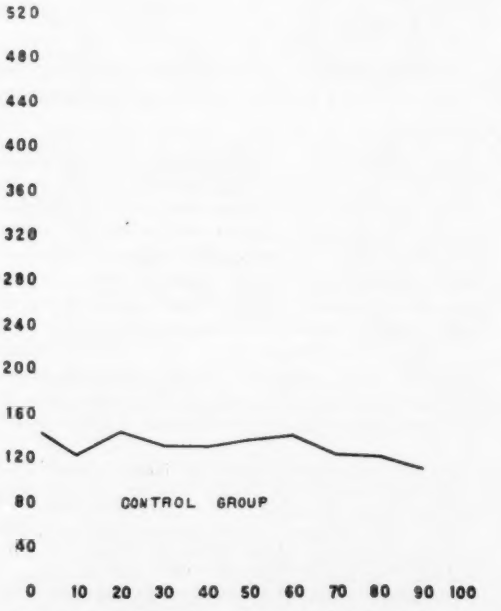



Fig. 4. Control group—no change in cholesterol values.

Fig. 5. Extensive and marked atherosclerotic changes in aortas from Group B (high cholesterol diet plus posterior lobe extract).

Fig. 6. Microscopic section from an aorta of Group B showing extensive cholesterol deposit.

Fig. 7. Coronary artery from a rabbit of Group B showing extensive cholesterol deposit.

*Group C.*—This group of ten rabbits was placed on a normal laboratory diet the same as the control group and, in addition, received daily 1 cc. of posterior lobe extract.

The first week the injections were given twice a day and following this, once a day over a period of 100 days so that the average amount injected was 107 cc. of posterior lobe extract.

A composite curve of the cholesterol estimations made every ten days on each group shows that the cholesterol curve rises quickest and highest in Group B (high fat diet plus posterior lobe extract) reaching close to 480 mg. (Fig. 1). Group A (high fat only) reaches 440 mg. (Fig. 2).

Group C (posterior lobe extract) shows a small initial rise and then flattens out. (Fig. 3). This is similar to the control group (Fig. 4) and indicates that the extract did not have an appreciable effect on the blood cholesterol.

In examining the aortas, it was found that those of Group B showed the most intense and extensive atheromatous deposits, exceeding by far those in the other groups. (Fig. 5).

These aortic atheromatous deposits are readily seen in the microscopic sections (Fig. 6).

The coronary arteries of this group also show an equal extensive atheromatous deposit (Fig. 7).

The aortas of Group A (high fat diet), while showing atheromatous deposits, did not compare in intensity with those of Group B (Fig. 8). This is verified by a study of the microscopic sections (Fig. 9). The aortas of Group C showed only slight deposits. These were not uniform but some (aorta on right in Fig. 10) equalled those of Group A.

Since the adrenal cortex is a factor in cholesterol-steroid metabolism, it is of interest to note the changes in the adrenal weights as well as in the microscopic picture of these groups.

### Average Adrenal Weights

| | |
|---|---|
| *Control Group* (Normal Diet) | 278 mg. |
| *Group C* (Normal Diet plus posterior lobe injections) | 415 mg. |
| *Group A* (High Fat Diet Only) | 435 mg. |
| *Group B* (High Fat Diet plus posterior lobe injections) | 639 mg. |

The adrenal weight correlated with the body weight (combined weight of adrenals divided by body weight multiplied by 100,000) gave the following adrenal indices:

| | |
|---|---|
| *Control Group* (Average Index) | 22.948 |
| *Group C* (Normal Fat Diet) | 37.52 |
| *Group A* (High Fat Diet) | 38.52 |
| *Group B* (High Fat Diet plus injections) | 54.845 |

On microscopic section, the control group showed no changes in the adrenals (Fig. 11).

The adrenal cortex of Group A showed extensive lipoidosis with hypertrophy indicating increased activity (Fig. 12).

Fig. 8. Aortas of Group A (high cholesterol diet) showing atheromatous deposits.

Fig. 9. Microscopic section from aorta of Group A.

Fig. 10. Aortas of Group C (normal diet plus posterior lobe extract) showing slight atheromatous deposits.

Fig. 11. Adrenal cortex of control group (normal).

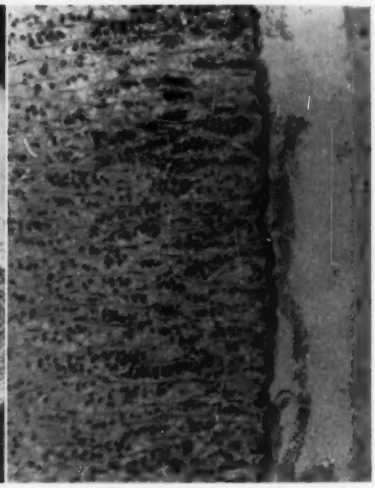


Fig. 12. Section of adrenal from Group A showing lipoidosis.

The adrenals of Group B showed marked lipoidosis with enlargement of the glomerular zone. They gave the appearance of extreme exhaustion from excessive stimulation (Fig. 13).

The kidneys from Group B showed marked interstitial lipoidosis with areas resembling the fat calcium infarct of the kidney papillae described by Aschoff. There was well marked arteriolar degeneration with localized areas of round cell infiltration fibrosis of the tubules and glomeruli and retraction of the kidney capsule (Fig. 14).

The ovaries of Group B showed extreme lipoidosis of the ovarian stroma which has undergone a uniform change somewhat resembling the adrenal cortex and corpus luteum. There was extreme overloading of all stroma cells with fat. There were many ripened and ripening follicles. The follicular tissue had been pushed to the extreme rim of the organ just beneath the capsule by the hypertrophic lipoid stroma (Fig. 15).

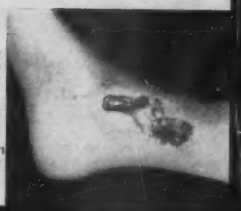
It is evident from the foregoing that those rabbits receiving posterior lobe injections have a much greater adrenal weight than the non-injected groups. This

*(Turn to Page 99)*

FORCE INJURY
severe bruises
... swelling
... cleared
by fifth day[2]

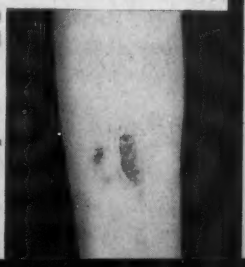


VARICOSE
ULCER
15 years duration
... resolved with
VARIDASE[1]

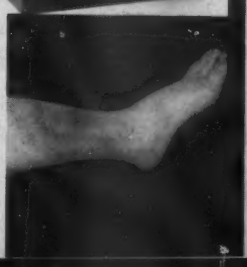


INFLAMMATORY
DERMATOSIS
rapidly spreading
rhus dermatitis
healed within
a week[1]

INFECTED
LACERATION
marked reversal
in 3 days...
returned
to school...
closure advanced[1]



THROMBOPHLEBITIS
back on his feet
in a week after
recurrent episode[1]



REFRACTORY
CELLULITIS
normal routine
resumed after 4 days
of VARIDASE[1]

Fig. 13. Section of adrenal from Group B showing enlargement and lipoidosis with extreme exhaustion.

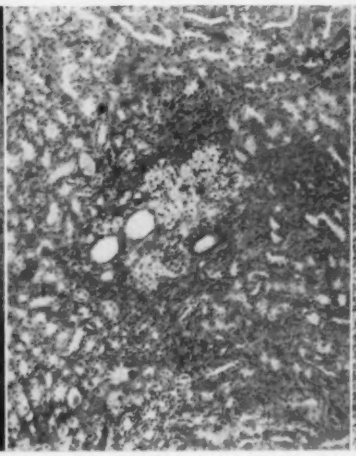


Fig. 14. Section of kidney from Group B showing marked lipoidosis-central area showing fatty infarction.

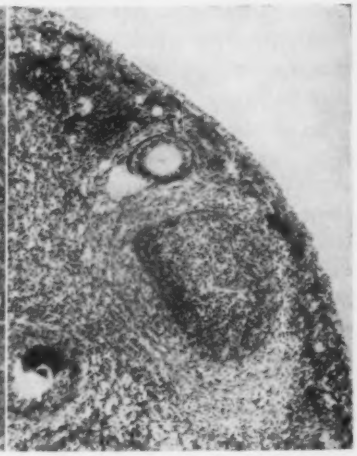


Fig. 15. Section of ovary from Group B showing lipoidosis, areas of extreme overloading of stroma cells with fat, many follicles near surface beneath capsule.

*(Continued from Page 94)*

is also seen in the average adrenal indices. Group C, on a normal diet plus the injections of the extract, had an average increase over the control group of 137 mg. Group B, on a high fat diet plus the injections, had an average increase of 204 mg. over the group on high fat diet alone, and an average increase of 361 mg., over the controls. The increase shown microscopically was confined to the cortex.

The vascular changes show that the factor which produced the greatest pathologic atheromatous change was the posterior lobe extract. Thus, there is a vasoconstrictor factor in addition to the cholesterol which produced the most prominent vascular changes.

The enlargement and increased weight of the adrenals receiving posterior lobe injections, even without a high cholesterol diet, requires explanation. Recent work[7,16] indicates that this extract activates the anterior pituitary to release ACTH with subsequent increase in the size and weight of the adrenal.

There are embryologic, anatomic and physiologic connections between the hypothalamus, and the posterior and anterior pituitary. There is evidence[6] indicating that the hypothalamus can release posterior lobe hormone which, in turn, activates the adrenal cortex. Goodman and Gilman stated that "It is generally accepted that the stimulus for the release of hormone arises in the hypothalamic nuclei." They go on to say that "there is strong evidence which indicates that the hormone is formed by the nerve cells in the supra-optic and paraventricular nuclei of the hypothalamus." The hormone then passes along the nerve fibers into the neurohypophysis and accumulates in the perivascular areas around the terminations of the nerve fibers. It seems most likely that stress and strain, shock, infections, severe trauma, toxemias, and other conditions set the hypothalamic-pituitary (posterior and anterior) mechanism into activity. These stresses set the whole mesodermal defense forces into action, not the least of which is the immune mechanism, the reticulo-endothelial system. It is well known that such stress conditions activate the pituitary gland, and in the growing child, the osseous system is stimulated, and rapid growth results.

Chronic stress and worry, therefore, are likely to result in hypertension and arteriosclerosis. Conditions and diseases which chronically activate the hypothalamic-pituitary system are likely to be the prime factors in hypertension and arteriosclerosis. The wear and tear on the nervous-vascular system as part of our daily living is due, in part at least, to the varying secretion of the posterior lobe's vasoconstrictor effect on the vascular system.

There are other facts which lend support to the pituitary's influence in atherosclerosis. For instance, it is known that the posterior pituitary hormone is able to overcome insulin hypoglycemia.[8,11] A rabbit receiving 80 units of regular insulin almost always dies with hypoglycemic convulsions but the injection of 1 or 2 ml. of posterior lobe extract restores the animal's blood sugar to normal and recovery ensues. This may be understood by the release of ACTH from the anterior lobe since this hormone is an activa-

tor of carbohydrate metabolism. This suggests the close relationship which exists between the posterior and anterior lobe, carbohydrate metabolism and the great frequency of atherosclerosis in diabetes mellitus.

An additional step in understanding this relationship is the fact that epinephrine also has the ability of overcoming insulin hypoglycemia. Does the epinephrine overcome the insulin hypoglycemia by stimulating the hypothalamus via the sympathetic fibers thence to the posterior lobe and, as stated, activation of the anterior lobe with release of ACTH? Attention is called to the fact that the posterior lobe is an ectodermal nervous tissue derivative and responds to nervous impulses, whereas the anterior lobe is also an ectodermal derivative but originates from Rathke's pouch.

Borchardt[2] found that posterior lobe extracts produce glycosuria. Excitation of the superior cervical sympathetic ganglion can produce glycosuria. This has been attributed to pituitary hyperfunction.[4]

Many years ago (1914)[9] it was stated that the pituitary gland has a selective action on the mesodermal tissues. Subsequent articles enlarged upon this.[10,12,13] Today the pituitary-mesodermal (mesenchymal) relationship is discussed as "collagen diseases." The discovery of ACTH and cortisone brought this relationship into the foreground.

As related to the present article of the pituitary gland in the production of atherosclerosis, overactivity of this gland would result in mesodermal connective tissue overgrowth in the vascular layers, contraction of the smooth muscle, activation of cholesterol (fat) and carbohydrate metabolism. Mention is made of the well-known diabetes mellitus seen in overactive pituitary states such as acromegaly, gigantism, and basophilism.

Basically, the pituitary in acromegaly and gigantism produces a marked development of the mesodermal vascular system, as well as an increase in the mesodermal blood volume; otherwise, no growth would ensue. This is well illustrated in the osteitis deformans of Paget in which disease there is as much as twenty times the normal increase of blood flow in the affected bones resulting in an overgrowth of the osseous system with increased local bone temperature (Edholm, Howarth and McMichael).[5]

Finally, Krogh and Rehberg's earlier work on the posterior lobe secretion and capillary tone bears repeating.[8] They found that in amphibians, the tone of the capillaries and arterioles was controlled by the posterior lobe secretion. Hypophysectomy in amphibians caused marked capillary and arteriolar dilatation and an increase in capillary permeability to saline solutions, with the rapid formation of edema; in the toad, a 40 per cent fall in blood pressure, which is not observed after removal of the pars distalis alone, or a lesion in the tuber. The blood pressure level is restored by the injection of posterior lobe extract.

## Summary

In the article previous experimental data showed that the most extensive atheromatous changes were found in the group of rabbits which were fed on a high cholesterol diet and received, in addition, injections of posterior pituitary extract for a period of 100 days. Extensive changes were found in the aorta, coronary arteries, and kidneys. The group of rabbits receiving only a high fat diet and no injections of extract did not show vascular changes in any comparable degree. The serum cholesterol estimations showed that while the group on a high cholesterol diet had a marked rise, the high cholesterol diet *plus* the posterior lobe hormone injection produced the quickest rise and highest cholesterol curve. Furthermore, the adrenal weights showed striking differences. They were as follows:

Average Adrenal Weights

| | |
|---|---|
| *Control Group* (Normal Diet) | 278 gm. |
| *Group C* (Normal Diet plus posterior lobe extract) | 415 gm. |
| *Group A* (High Fat Diet Only) | 435 gm. |
| *Group B* (High Fat Diet plus posterior lobe injections) | 639 gm. |

Thus it shows that under the conditions of the experiment, those rabbits receiving posterior lobe injections (Groups C and B) have a much higher adrenal weight than the non-injected group. This same difference is evident in the adrenal weight-body weight indices.

| | |
|---|---|
| *Control Group* (Average) | 22.948 |
| *Group C* | 37.52 |
| *Group A* | 38.52 |
| *Group B* | 54.845 |

The increase was confined to the adrenal cortex.

The aforementioned vascular changes of greatest degree, as well as the greatest adrenal weights and body indices, were in the two groups receiving posterior lobe extract.

It is evident that besides a cholesterol element, a vaso-constrictor element played a major role in producing the greatest vascular and adrenal cortex changes.

The ovaries of the high cholesterol-pituitary injected group showed extreme lipoidosis of the ovarian stroma, with changes resembling the adrenal cortex and corpus luteum.

The relationship of both the anterior and posterior pituitary lobes to the mesoderm helps to explain the role of this gland in the production of atherosclerosis.

Furthermore, both anterior and posterior lobes of the gland play a role in carbohydrate metabolism thus adding a link to the explanation as to why the diabetic patient is so frequently afflicted with atherosclerosis.

The embryologic, anatomic, and physiologic relationship between the sympathetic nervous system, the hypothalamico-pituitary-adrenal cortex mechanism adds to the understanding of how chronic stress, infections, toxemia, trauma, and shock would lead to atherosclerosis.

## References


1. Aschoff, Ludwig: Lectures on Pathology. New York: Paul B. Hoeber, 1924.
   (a) p. 131, (b) p. 132, (c) p. 152-153.
2. Borschardt, L.: Experimentelles über den Diabetes bei der Akromegalie. Deutsche med. Wchnschr., 34:946-947, 1908.
3. Burn, J. H.: Modification of action of insulin by pituitary extract and other substances. J. Physiol., 60:69-78, 1925.
4. Cushing, Harvey: Papers Relating to the Pituitary Body, Hypothalamus, and Parasympathetic Nervous System. p. 34. Springfield, Illinois: Charles C Thomas. 1932.
5. Edholm, O. G., Howarth, Sheila, and McMichael, J.: Heart failure and bone blood flow in osteitis deformans. Clin. Sc., 5:249-260 (Dec.) 1945.
6. Goodman, Louis S., and Gilman, Alfred: The Pharmacological Basis of Therapeutics. Second Edition. p. 869. New York: The Macmillan Co., 1955.
7. Harris G. W., and Fortier, Claude: The Regulation of Anterior Pituitary Function with Special References to the Secretion of Adrenocorticotrophic Hormone, *In:* Fourth Annual Report on Stress. pp. 106-127. Montreal, Canada: Acta Inc. 1954.
8. Krogh A., and Rehberg, P. B.: The influence of the hypophysis upon the tonicity of the capillaries. Comp. rend. Soc. de biol. (Paris), 87:461-463, 1922.
9. Moehlig, Robert C.: A study of the ductless glands. Detroit M. J., 14:268-289, 1914.
10. Moehlig, Robert C.: Ductless Gland Cell Control. Monograph. Townsend Press. 1918.
11. Moehlig, Robert C., and Ainslee, Harriet: Antagonistic action of posterior pituitary extract and insulin, J.A.M.A., 84:1398-1400 (May 9) 1925.
12. Moehlig, Robert C.: Embryohormonic relations of the pituitary gland to mesenchymal tissues. Am. Int. Med., 1:563-576 (Feb.) 1928.
13. Moehlig, Robert C.: Embryohormonic relations of endocrine glands; relations of pituitary gland to mesodermal tissues. J. Michigan M. Soc., 31:656-667 (Oct.) 1932.
14. Moehlig, Robert C.: Role of posterior pituitary gland in experimental production of atherosclerosis. Endocrinology, 14:337-342 (Sept.-Oct.) 1930.
15. Moehlig, Robert C., and Osius Eugene: The pituitary factor in arteriosclerosis. Its experimental production in rabbits. Ann. Int. Med., 4:578-592 (Dec.) 1930.
16. Pickford, Mary: The action of acetylcholine on the supraoptic nucleus of the chloralosed dog. J. Physiol., 106:264-270, 1947.


*964 Fisher Building*

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## CONGENITAL ARTERIOVENOUS COMMUNICATION

*(Continued from Page 81)*

factor determining the rare discovery of such lesions. Except for a chance routine x-ray, this man might have lived a long time without the discovery of his condition.

Previous articles on A-V communications have included the suggestion that complete removal of the lesion is probably the most satisfactory method of dealing with the problem. Our experience with this patient concurs in this judgment.

The last point of interest is one of histopathologic concern. Under microscopic surveillance, the structural similarity of congenital A-V communication to that of hemaingioma creates a major difficulty in identification without previous knowledge of the history of the case. Therefore, the pathologist has to be informed of the clinical findings in order to arrive at a compatible diagnosis.

## Summary

1. A congenital A-V communication of an unusual location is reported.

2. Some of the difficulties of differential diagnosis as well as histopathologic diagnosis are discussed.

## References


1. Bailey, F. R.: Text-Book of Histology. Revised edition. Baltimore: The Williams & Wilkins Co., 1948.
2. Beno, T. J., and Das, R.: Familial arteriovenous aneurysm of the lung: Incidence in mother and son. Ann. Surg., 146:830, 1957.
3. Bertelsen, A. John: Congenital A-V communications of extremities. Acta. chir. scandinav., 105:448, 1953.
4. Fisher, H. C., and Johnson, M. F.: Congenital arteriovenous communication. Am. Surgeon, 23:112, 1957.
5. Pratt, G. H.: Cardiovascular Surgery. Philadelphia: Lea & Febiger, 1954.

# Mitral and Aortic Stenosis

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## Mitral Stenosis

OF ALL forms of acquired heart disease, mitral stenosis has been most effectively treated by surgical methods. Basically, mitral stenosis is a mechanical lesion and might therefore be expected to yield to mechanical methods. It is almost always the late result of rheumatic heart disease. The defect consists of fusion of the free edges of the bicuspid valve leaflets, and scarring and contracture of the leaflets and the valve ring. The effect of this is to reduce the size of the opening between the left auricle and the left ventricle so that the volume of blood which can pass into the ventricle during diastole is slowly but progressively reduced. As this occurs over the years, there is a typical and logical sequence of progressive disability. At first, when the stenosis is of such size as to limit the diastolic flow of blood only in the upper ranges of required volume flow, the patient notices limitation of exercise tolerance only during periods of greatest activity. As the stenosis increases there is progressive limitation of exercise capacity to the point where minimal amounts of exercise may be difficult or impossible. Conditions which normally increase the cardiac output, such as pregnancy, fever, and emotional stress, produce the symptom-complex of failure because the required increase in minute volume flow is impossible through the stenotic mitral valve.

Physiologically speaking, the obstruction at the mitral valve progressively raises the interauricular pressure, the pulmonary capillary pressure, the pulmonary artery pressure, and eventually the right ventricular pressure. Accordingly, there is enlargement of the left auricle, pulmonary edema, hypertrophic pulmonary arteriolar changes, and enlargement of the right ventricle. This latter may produce dilatation of the tricuspid valve ring with tricuspid insufficiency and right auricular and venous pressure rises, which, in turn, produce distention of the neck veins, enlargement of the liver and peripheral edema. Hence the symptomatology of "backward failure."

Inadequate flow into the left ventricle produces reduction in left ventricular output to the arterial system with the result that there is increasingly easy fatigability, coldness of the hands and feet, and gradual weight loss. These are of course symptoms of "forward failure."

About the stage when definite limitation of moderate physical exercise is encountered, it is common to observe irregularities of the cardiac rhythm, which eventually end in established auricular fibrillation. This irregularity further reduces the pumping efficiency of the heart and permits the formation of intra-auricular clots which may become free and be pumped into the arterial circulation where they produce embolic phenomena, manifestations of which depend upon the size and the chance lodgment of the embolus. The results of these vary from permanent hemiplegia or extremity loss to inconsequential small areas of infarction.

Our experience with the surgical correction of this lesion over the past eight years is that mitral commissurotomy offers a very significant improvement in about four out of five of all cases operated upon.

The ideal time for the operation is when the patient begins to have clear-cut exercise tolerance limitation. If a patient cannot ascend a full flight of stairs without stopping to breathe and if he cannot walk a full block at a normal pace, the valve opening is then just slightly larger than finger tip in size. Withholding the operation permits further deformity and calcification of the valve cusps, which may render correction less effective. If auricular fibrillation has not already

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occurred, deferring operation may permit the onset of this arrythmia with the attendant risk of arterial embolization. In addition, delay in correction may permit the pulmonary vascular changes to be so extensive that they are irreversible.

If a patient with mitral stenosis has had one or more arterial embolic episodes, the operation should be carried out forthwith since following recovery from commissurotomy, embolization is very rare and the chance of a second embolus in a patient who has had one is very high unless operation is done. The reason for this is that the clots tend to form in the recesses of irregular auricular appendages of patients in auricular fibrillation, and if a patient has had one embolus he has an established nidus for clot formation and he is much more likely to have another embolism than a patient who has never had one.

In considering the desirability of operative correction of mitral stenosis, the matter of other valvular involvement must, of course, be assessed. Although many cases of almost "pure" mitral stenosis do occur, many patients exhibit some degree of mitral regurgitation and may also have other valve involvement, the most common being aortic stenosis or regurgitation. At the present time, it is our impression that moderate degrees of either aortic regurgitation or mitral regurgitation do not contraindicate mitral commissurotomy for stenosis, if the stenosis is the predominant lesion.

The mortality risk of mitral commissurotomy done in a patient who has not progressed to the point where he is in chronic failure, is below 5 per cent. This compares favorably with the over-all risk of biliary surgery, and is less than the annual risk of maintaining these patients on a nonoperative regime. The percentage of significant improvement following commissurotomy in properly selected cases is about 85 per cent.

Studies of late results have shown that the postoperative group maintain a very favorable status during the subsequent years. It is known that a certain deterioration of technically well done cases may occur in a small percent and be due to certain facts. The first is the progress of other valvular lesions, such as aortic stenosis, aortic regurgitation, or mitral regurgitation. The second is restenosis of the valve cusps. This occurs in about 5 per cent of patients and may be apparent two or three years after the commissurotomy. Our experience with re-operating on these patients, so far, is that the mortality risk is no higher and the functional results of re-operation have been satisfactory.

In the past, we have judged that open cardiotomy with the pump oxygenator is not justified for mitral stenosis but with our increasing experience in this field, certain complicated situations of stenosis and regurgitation may well be better treated by the open approach.

## Aortic Stenosis

Aortic valvular stenosis is also an acquired valvular disease which is amenable to surgical correction. Although the fundamental anatomic and physiologic defect is the same as in mitral stenosis (in the sense that with increasing aortic stenosis there is increasing obstruction to flow during the period when the valve is open), the secondary physiologic effects and course of the disease is very different. As the stenosis increases there may be very marked thickening and calcification of the valve cusps, and late in aortic stenosis, the valve may be very deformed, having the appearance of an irregular hard tile with a tiny opening somewhere near the center. The calcification and connective tissue scarring may also involve the openings of the coronary arteries, which impose the burden of insufficient coronary artery flow on the already overworked left ventricular muscle.

It is an interesting fact that the ventricular muscle by increasing its work and by subsequent hypertrophy, may so well compensate for the increasing stenosis of the valve that the patient may be quite unaware of any cardiac disability until quite late in the pathologic sequence. At first he may only notice palpitation or fatigue, and with no other warning than this may have the experience of fainting during a period of physical exertion, owing to lack of forward flow. The life expectancy when periods of syncope have appeared is less than one year. Unlike mitral stenosis, when these patients go into an episode of failure they are not easily brought out of it by rest and medicine —simply because it is nearly impossible to reduce the work of the left ventricle, which must, with each beat, force a volume of blood out through the tiny opening in the valve. The prognosis for a patient with aortic stenosis who goes into failure is very poor, unless, of course, some real correction of the valve opening can be made. It is an unusual patient who can be returned to gainful occupation by medical means alone after an episode of failure from aortic stenosis.

The correction of this serious situation naturally appeals to the surgeon. Our experience and that of others is that if these patients are operated on before

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# Changing Concepts in the Treatment of Endometriosis

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THE literature on endometriosis being particularly voluminous, it is easily understood why some important papers on this subject have escaped attention. For instance, at about the time the very significant work of Sampson was read and published, there appeared a case report in German by Brakemann that has gone unnoticed for many years. Twenty years ago, Joe Vincent Meigs wrote an editorial on his ideas of the etiologic factors in endometriosis; the ramifications of his theory have led to important therapeutic steps in the management of endometriosis.

In 1945, Cashman published a significant series of cases on a particular type of treatment for endometriosis; the full implications of his work have too frequently escaped serious thought. Ten years ago, Karnaky brought out a medical regimen for treating endometriosis that was not taken seriously. These names: Brakemann, Meigs, Cashman and Karnaky—are brought out because, as time goes on, their work takes on an increasing significance. To better understand our current therapy used in treating endometriosis, we might reconsider for a moment what presumably is the etiology of this strange disease. In 1898, Iwanoff was the first to suggest that the endometrium-like tumors in and on pelvic peritoneum were due to metaplasia of the mesothelium or serosal layer of the uterus. This serosal theory or metaplasia factor received support from Robert Meyer in 1919, and is based on the fact that all epithelia of the female genital system are derived from the celomic epithelium of the urogenital folds, which in turn comes from the primitive peritoneum. There are many undeveloped cells of this peritoneum remaining in the adult female viscera and to these Robert Meyer ascribed certain differentiating potential which could make them the anlage of endometriosis. He believed the typical lesions developed in response to an inflammatory reaction. Later on, Novak accepted the Iwanoff-Meyer Metaplasia Theory but felt that there was an unknown endocrine factor at work which initiated late differentiation.

Meigs, in 1938, advanced the theory of etiology on which we have been able to build a conservative therapeutic plan. He noted that endometriosis was common in private patients who married late and among whom contraceptive practices were widespread. By contrast, endometriosis was a rarity in ward patients in whom marriages took place earlier and contraceptive practices were practically non-existent. He theorized that the interruption of the rhythmic ovarian changes in aberrant endometrium by repeated early pregnancies must be beneficial and, conversely, that prolonged periodic menstruation, without interruption favored the development of endometriosis. Thus, the Meigs theory supplied the "unknown endocrine factor" suggested by Novak. Recently, Roger Scott has shown with his work on the monkey that ectopic endometrium will not bleed unless it is subjected to cyclic progesterone withdrawal, using a plan of administering both estrogen and progesterone in a pattern similar to that of menstruation. This brings added proof to the original thoughts of Meigs on etiology.

## Treatment

Conservatism must be uppermost in our minds while treating this disease since we are confronted with a non-neoplastic entity affecting women in the reproductive years. One should keep in mind the Meigs concept of etiology and realize that it offers a framework for a conservative therapeutic plan for endometriosis. In addition, one must remember that we have very effective treatment methods well documented in the literature that have been regarded too lightly in the past. I would call attention again to the work of Brakemann, who in 1924 did a *hysterectomy only* for the treatment of an endometriosis of the bladder. In all, we have found twelve case reports of endometriosis of the genito-urinary tract being cared for in this fashion by various German gynecologists. Surely, Cashman was unaware of Brakemann's pioneer effort when he published over

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130 case reports in which hysterectomy alone was employed for the treatment of external endometriosis.

*Pregnancy.*—A married patient should be advised to become pregnant when found to have endometriosis. Physiologic amenorrhea causes a regression in aberrant endometrium that is truly remarkable. In the most severe cases of endometriosis, one is hard put to palpate the lesion beyond twelve weeks of pregnancy. I have never seen a case of endometriosis that did not respond favorably to pregnancy. At full term, the cul-de-sac (and other areas previously so deeply involved) will present white, soft, puckered clusters of peritoneum. This same appearance is often noted in the pelvis of postmenopausal women.

In severe cases of endometriosis which have been quiescent during pregnancy, symptoms and palpable nodules may recur as early as the second postpartum period. A second pregnancy has proved to be most helpful in preventing a recurrence of symptoms; most women will remain symptom-free, while in a small percentage the pain may recur after varying periods of time.

*Stilbestrol.*—There are women with endometriosis who are infertile or in whom pregnancy is out of the question. For these we have a "pregnancy equivalent"—amenorrhea produced by progressively higher doses of stilbestrol. This treatment, which was suggested by Karnaky, although slow to catch on in this country, has great merit. The dosage table I use is a modification from Karnaky and is as follows:

Start after a menstrual period:

stilbestrol 0.5 mg. for five days
stilbestrol 1.0 mg. for five days
stilbestrol 2.0 mg. for five days
stilbestrol 4.0 mg. for five days
stilbestrol 10.0 mg. for five days
stilbestrol 25.0 mg. for five days

The 25 mg. dose is maintained until spotting occurs at which time an additional 25 mg. is added to the daily dose; 25 mg. more are added each time spotting or "break through" bleeding is noted. The average dose needed to maintain amenorrhea is 300 mg. a day.

Stilbestrol is abruptly stopped after nine or ten months and withdrawal bleeding may occur but has not been severe. Medically-induced amenorrhea seems to produce the same regression in endometriosis as that induced by pregnancy. It is particularly fitted to patients with marked cul-de-sac involvement. The favorable response lasts about as long as that from pregnancy.

*Testosterone.*—Testosterone has been employed in the treatment of endometriosis without striking success. This is due, I believe, to the low dosage which must of necessity be maintained. The masculinizing effect of testosterone is well known, as is the unpredictability of the dose producing these changes. Although most of these secondary changes are reversible, the voice change is permanent. These troublesome features leave testosterone with little place in the treatment of endometriosis.

*Surgical Treatment.*—Favorable response from pregnancy or stilbestrol has reduced considerably the need for surgery in endometriosis. If a young woman fails to respond to these two measures or refuses to undertake further treatment by amenorrhea, the endometrial implants should be resected and a presacral neurectomy and ovarian neurectomy performed. Extirpation of any organ for endometriosis in young women is not often necessary. This applies particularly to the ovary.

Surgical exploration must be carried out in patients with endometriosis who have bilateral or unilateral ovarian enlargement greater than 5 cm. in diameter because it is impossible to differentiate ovarian endometriosis from true neoplasms by physical examinations alone. Treatment of ovarian endometriosis is different from that of true tumors of the ovary for which cystoophorectomy is practically always necessary. Endometriomas of the ovary are dissected free from their adhesive beds and bisected at a point opposite the hilus. The cyst contents are evacuated and the cyst lining gently dissected away leaving as much normal tissue as possible. Extensive alteration in ovarian function might be suspected from the great distortion when the ovary is enlarged many times by blood-filled cysts, but when the cysts are resected there is enough normal tissue to maintain adequate function, that is, ovulation and conception. In rare instances, castration might be necessary, but should not be considered without a trial of conservative measures first.

With women in the late childbearing years or women with several children, the foregoing therapeutic steps are frequently not feasible. It was in this group that Cashman advised hysterectomy with conservation of the ovaries. This is a highly successful treatment and again, amenorrhea is produced—this time permanently. I have observed all manner of

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# Acute Tubular Necrosis

## *Conservative Management and the Artificial Kidney in Treatment*

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ACUTE renal failure is a clinical syndrome resulting when renal excretory function is rapidly lost. One of the most common causes of acute renal failure is acute tubular necrosis. It is produced by a sudden decrease in the renal circulation by such incidents as incompatible blood transfusion, intravascular hemolysis and hypotension. The clinical course is characterized by a period of oliguria followed by a recovery phase. Since this is a reversible lesion, early recognition and proper management are extremely important.

### Differential Diagnosis

The first sign of impending acute renal failure is a low urine output. It is therefore imperative that accurate intake and output records be maintained on all patients who have had hypotensive episodes, incompatible blood transfusions, or exposure to chemical nephrotoxins. Once oliguria or anuria is recognized, it becomes important to determine the etiology.

*Immediately Reversible Lesions.*—There are several conditions, producing low urine outputs which are immediately reversible, if promptly recognized and corrected.

1. *Hypotension* must be reversed immediately or the kidneys may develop acute tubular necrosis.

2. *Salt and water depletion* may be indicated by low urine output with high specific gravity. Where this factor is a possibility a rapidly administered salt or water load, depending on the clinical circumstances, is indicated. In a dehydrated patient the administration of a 1,000 cc. of 10 per cent glucose in water in a one-hour period is a good therapeutic test. If an increased urine output is observed, it suggests that dehydration is the etiology of the oliguria.

3. *Obstructive uropathy* must be considered in patients where the following circumstances are present: (1) anuria, (2) marked daily fluctuations in urine output, (3) absence of other predisposing causes of acute renal failure, and (4) urine specific gravity of 1.018 or greater. All patients that fall into these categories should have early cystoscopy and bilateral ureteral catheterization.

When the immediately reversible causes of oliguria, have been ruled out, an organic renal lesion is undoubtedly present and the following entities must be considered: (1) the acute glomerulitides, such as acute glomerulonephritis, periarteritis nodosa, acute lupus erythematosus and hypersensitivity angiitis secondary to such drugs as the sulfonamides or penicillin, (2) acute pyelonephritis or necrotizing papillitis, (3) acute exacerbation of pre-existing renal disease, (4) lesions of the great renal vessels such as renal artery emboli or thrombosis of the renal artery or vein, (5) acute tubular necrosis or (6) bilateral cortical necrosis.

### Clinical Course

The clinical course of acute tubular neorosis is characterized by two arbitrarily defined phases, the oliguric phase in which the urine output is less than 400 cc. during a twenty-four-hour period, followed by the diuretic phase in which the urine volume is above this figure. The oliguric phase may vary from several days to three weeks in duration, during which time the patient gradually develops the signs and symptoms of uremia. It is during this period that hypervolemia and hyperkalemia may develop and lead to the complications of pulmonary edema and potassium intoxication. These two complications are the most frequent causes of death during the oliguric phase.

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Gradual increases in the daily urine output characterize the diuretic phase. Despite the apparent improvement, approximately 25 per cent of the deaths in this syndrome occur during this phase. If the patient can be successfully carried through this clinical course, almost complete recovery of renal function can be expected within a six to eight-month period.

## Treatment

Since the renal regulation of the composition and volume of body fluids is lacking, therapy must be directed at the control of these parameters. In addition to the renal failure these patients often have associated trauma, operative complications, or other factors that greatly complicate their management.

*Water Balance.*—Hypervolemia leading to pulmonary edema is a common fatal complication and is produced by overloading the patient with fluids. The usual adult loses about 0.5 cc. per kg. per hour or 700 to 800 cc. of fluid per day through the skin and lungs (insensible loss). The water of oxidation, produced by the metabolism of body fat, protein and carbohydrates, amounts to approximately 200 to 400 cc. per day and must be subtracted from the insensible loss when determining fluid balance. Therefore, the daily fluid requirement in the average adult amounts to about 400 to 500 cc. of water plus enough additional water to replace the daily urine output. If there is extra-renal fluid deficit, such as gastrointestinal loss, this must be replaced on a volume for volume basis. The composition of the replacement solution may be determined by analyzing a twenty-four-hour aliquot for sodium and chloride and replacing these electrolytes in the amount they are lost. Potassium must not be included in the replacement therapy.

The accuracy of the calculated daily fluid replacement may be checked by the observation of the clinical status of the patient and, most important, by daily weights. Since these patients are getting inadequate calories to maintain body weight they should lose approximately 0.5 kg. (about one pound) of weight per day. If they fail to do this, the patient is being overhydrated.

*Caloric Requirements.*—It is important that a certain amount of calories be given to these patients to minimize protein breakdown and prevent starvation ketosis. At least 100 gm. (or more, if possible) of carbohydrate should be given daily. If the patient can tolerate oral feedings the carbohydrate may be given as hard, rock candy since this is pure glucose. If intravenous feedings are necessary, the glucose may be given as a hypertonic solution. In order to give this amount of glucose in the limited fluid allowed the patient, at least a 25 per cent solution of glucose in water is required. The irritating properties of this solution make it necessary to administer it in a large-caliber vein. This is best accomplished by passing a polyethylene catheter into an upper extremity vein so the tip of the catheter lies in the subclavian vein. The solution is dripped in very slowly over a twenty-four-hour period. The catheter must be changed to another vein every five to six days to minimize phlebitis at the cut-down site.

*Electrolyte Management.*—1. *Potassium*: The danger of potassium intoxication makes it imperative that no potassium be given to these patients. The breakdown of body tissue releases potassium into the extracellular fluid. Since the kidney cannot excrete the potassium in acute renal failure, the plasma concentration gradually increases to toxic levels. This toxicity is manifested by its effect on cardiac muscle producing characteristic changes in the electrocardiogram. These changes are indicated by a tenting and elevation of the T waves, followed by spreading of the QRS complex loss of the P wave, and finally, the development of a sine wave and ventricular fibrillation. Since the clinical manifestations of potassium intoxication develop rather late, the best methods of following this are by daily electrocardiograms and serum potassium determinations.

The best therapy for potassium intoxication is prophylaxis. Recently, with the introduction of the cation exchange resins of the sodium and hydrogen cycle, it has been possible to keep potassium levels in the normal range in almost all patients. These resins are polymers of carboxylic acid which are saturated with sodium or hydrogen ions and have an affinity for potassium. When the resin is placed in the gastrointestinal tract, ionization takes place and potassium is picked up by the resin in exchange for a hydrogen ion.

The resin may be given orally in the dosage of 20 gm. of resin dissolved in about 70 cc. of water or rectally as a retention enema of 20 gm. of resin in 200 cc. of water. This may be given as often

as is necessary to control the plasma potassium level.

The administration of hypertonic sodium solutions or hypertonic glucose with insulin is reserved for the treatment of acute potassium intoxication to tide the patient over until the resin will become effective. In certain instances the artificial kidney may be required.

2. *Sodium*: The daily loss of sodium in this group of patients is exceedingly small. It is unnecessary to give sodium unless there is an obvious extrarenal loss. It has been shown that the hyponatremia which frequently develops is largely due to expansion of the extracellular compartment and is a dilutional hyponatremia. It is seldom necessary to treat this unless the serum sodium falls below 120 mEq. per liter. If the patient is overhydrated the hyponatremia is treated by further restriction of fluid intake and increasing the insensible loss. If there is obvious sodium loss it may be replaced as it occurs.

3. *Bicarbonate*: As the acidosis ensues, the $CO_2$ combining power gradually falls. Since this is a compensatory mechanism to maintain body pH, it should not be treated unless it falls below a level of 12 millimols per liter and should not be corrected over 18 millimols per liter. Overzealous bicarbonate therapy may produce sudden elevations of the serum pH, with subsequent convulsions and death.

*Anemia.*—The anemia of acute renal failure is due to decreased erythropoesis, decreased red blood cell survival time and hemodilution. The anemia is best followed by frequent hematocrits and should not be treated unless it falls below 20 per cent. If transfusion is necessary, the administration of fresh, packed red cells is the treatment of choice since the patient needs the red blood cells and not the added plasma volume.

*Uremia.*—Aluminum hydroxide gels may be given orally to bind the phosphate ion in the gastrointestinal tract and decrease the plasma phosphate level. Testosterone proprionate in a dosage of 25 mg. intramuscularly daily may be helpful in minimizing the breakdown of body tissue. If nausea and vomiting become a problem they may be controlled by the use of thorazine or sparine given intramuscularly. In those instances where the symptoms of uremia are so severe that management of the patient becomes a problem, dialysis with the artificial kidney may be necessary.

*Infection.*—Great care must be taken to prevent sepsis in these patients because of their decreased resistence to bacterial invasion. All persons attending the patient should wear masks and gowns and wash their hands in a germicidal solution before examining the patient, to minimize the exposure of the patient to bacteria. Once the diagnosis of acute tubular necrosis has been established and if the patient is able to void, a urethral catheter is not needed and may only serve as a portal of entry for bacteria with fatal complications. Monilial infections, stomatitis and parotitis are common in these patients. Routine mouth care in the form of frequent mouth washes and brushing of the teeth is important in minimizing these complications.

Prophylactic antibiotics are probably of no benefit and may lead to super-infection, fungus infections or other complications. If clinical infection occurs it should be treated vigorously.

*Management of the Diuretic Phase.*—When the urine output per twenty-four hours exceeds 400 cc., the diuretic phase is entered and the urine output characteristically increases in a stepwise manner. Once the urine output exceeds 1200 cc. per twenty-four hours, supplemental potassium may be given. As the diuresis progresses, potassium depletion can rapidly develop and must be watched for with daily serum potassium determinations.

It is seldom necessary to administer more than 2,000 cc. of fluid over a twenty-four-hour period. During the diuretic phase, the body attempts to get rid of excess fluid accumulated during the oliguric phase. An attempt to keep up with the urine output by oral intake may lead to an excessive diuresis with large losses of electrolyte in the urine. Seldom should the diuresis exceed 3,500 cc. per twenty-four hours unless excessive water intake is present.

When the patient is able to take oral feedings and the urine output is over 1500 cc. per twenty-four hours, a low protein, high caloric diet may be instituted. The azotemia may continue to increase during the first three to five days of the diuretic phase, in spite of what happens to be an excellent urine output, and will then begin to fall to normal values. It is not necessary to correct the

anemia or acid-base balance as these factors will correct themselves as renal function improves. Any infection should be vigorously treated as the patient tolerates it poorly and this may be a fatal complication.

*Artificial Kidney.*—To understand the principles involved in the operation of the artificial kidney, the terms ultra-filtration and dialysis must be defined. If two solutions are separated by a membrane which is permeable to solute below a certain molecular weight (semi-permeable membrane), the permeable solute will pass from the solution in which it is in higher concentration across the membrane to the solution in which it is in lower concentration until equilibruim is established; this process is known as dialysis. If these two solutions and the interposing membrane exist in a closed, rigid system, a hydrostatic force applied to the solution on one side of the membrane forces both water and solute across the membrane; this process is known as ultra-filtration. All types of artificial kidneys are dialysers and some are both dialysers and ultra-filterers. In clinical situations, cellophane is the semi-permeable membrane on one side of which is the patient's blood and on the other side is an electrolyte solution whose composition is determined by the chemical status of the patient.

In 1913, Abel utilizing these principles described the first hemodialyser. In this apparatus, blood passed through hand-made collodion tubes, which were immersed in an electrolyte solution. This dialyser was not clinically applicable since (1) the pore size of the collodion membrane was extremely variable and allowed red blood cells to pass, (2) there was not a good anticoagulant available, and (3) the principles of renal physiology which are required to understand the management of the artificial kidney were not well known.

The purification of heparin and the availability of cellophane overcame two of the major obstacles to the development of the artificial kidney. Kolff utilizing these advances, in 1944, developed the first clinically applicable artificial kidney. This consisted of a drum around which was wrapped a continuous coil of cellophane sausage casing. The drum rotates so that the cellophane sausage casing through which the blood passes, is partially immersed in an electrolyte solution. This artificial kidney performs only dialysis.

In 1946, Skeggs and Leonards developed an artificial kidney consisting of two cellophane sheets sandwiched between rubber pads, the blood running between the cellophane sheets and the dialysing fluid running between the rubber pads and cellophane sheets as shown in Figure 1. Since this system is contained within a rigid framework, it is both a hemodialyser and an ultrafilterer and thus can remove both water and solute.

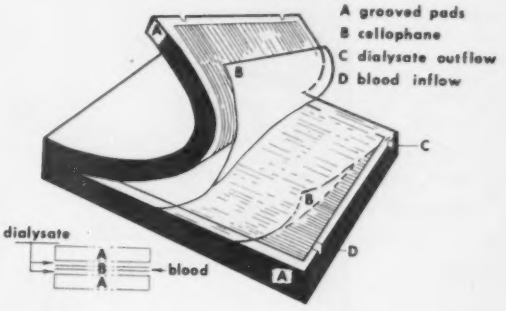


Fig. 1. Diagramatic illustration of the functional unit of the Skeggs-Leonards artificial kidney.

Recently Kolff has developed a disposable coil kidney which is also both a dialyser and ultrafilterer.

*Indications for Using the Artificial Kidney.*—Renal failure may be divided into two large classes, acute and chronic.

1. *Acute renal failure*: There are two major situations which should be considered as indications for the use of the artificial kidney during the course of acute renal failure: (1) potassium intoxication which cannot be controlled by the previously mentioned conservative measures and (2) severe symptoms of uremia.

2. *Chronic renal disease*: The delicate state of chemical equilibrium may be disturbed by trauma, infections, or acute exacerbation of the primary disease. The patient may be tided over this acute stress by hemodialysis with the hope that the previously existing state of equilibrium is re-established. In addition, patients with polycystic kidney disease are frequently benefited by dialysis when they first come for treatment with uremic symptoms.

3. *Non-renal indications*: Hemodialysis has also proven useful in cases of chemical intoxication such as salicylic over-dosage, bromism, barbiturate intoxication and severe non-renal metabolic acidosis.

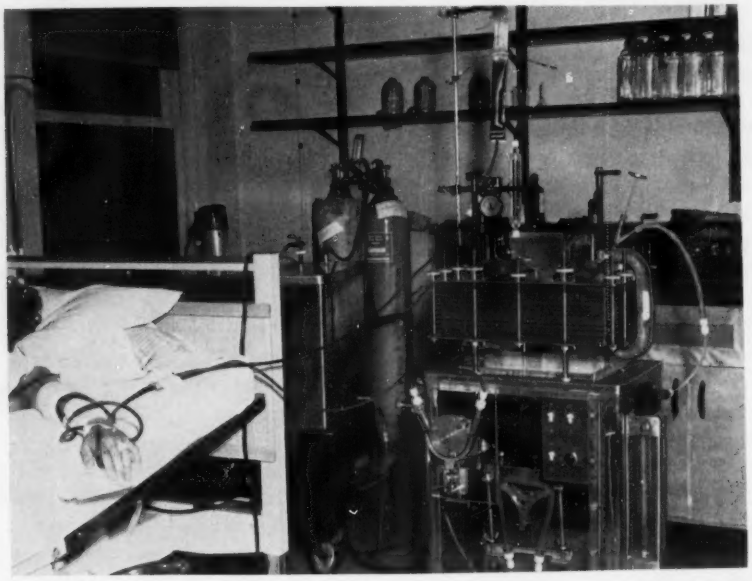

Fig. 2. The modified Skeggs-Leonards artificial kidney in use at the University Hospital, Ann Arbor.

*Contraindications to the Use of the Artificial Kidney*:—The chief contraindications to the use of the artificial kidney are persistent hypotension, severe bleeding, and terminal chronic renal disease.

*Organization of an Artificial Kidney Unit.*—The organization and operation of an artificial kidney unit is a complex problem requiring adequate laboratory facilities, especially trained technicians, and an experienced team of physicians familiar with the problems of renal insufficiency and the techniques of dialysis. This organization must be available at all times for the treatment of these patients. In addition, considerable time must be spent dialyzing experimental animals to establish and maintain a smoothly functioning unit.

With these problems in mind such a unit has been established at the University of Michigan Hospital and has been functioning over the past two years. This unit is fully equipped with both the Skeggs-Leonards (Fig. 2) and the Travenol twin-coil artificial kidneys (Fig. 3). The services of this unit are available to any physician desiring consultation or treatment of any patients with the complex problems of renal failure including hemodialysis.

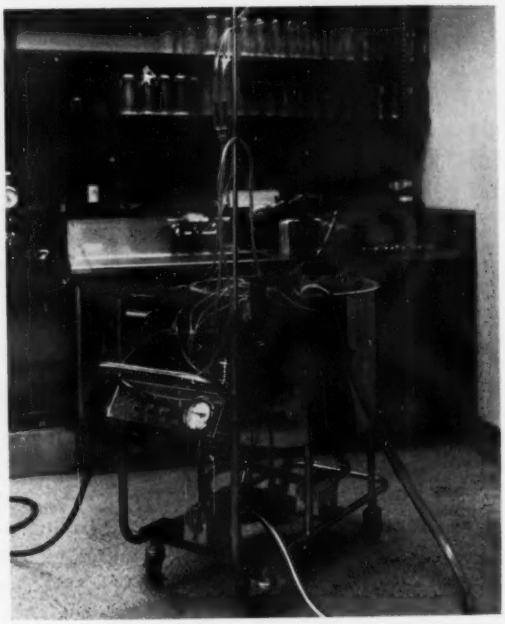

Fig. 3. The Travenol twin-coil artificial kidney.

# Health Insurance and the Medical Profession

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WHEN Blue Cross was timidly established in the middle 1930's, many groups, including medical societies, insurance companies and their acturaries, freely predicted that it would fail. It was argued that there would be no need for such insurance against sickness, and the cost would be excessive. However, the demand for prepayment for medical service surprised everybody. During the past ten years, Blue Cross has mushroomed into a billion dollar giant. Its growth has been surpassed in modern times only by television and prohibition bootlegging. Today, 50 million people have Blue Cross, and 123 million Americans—over 70 per cent of the population—carry some form of nospitalization insurance.[20]

In 1939, the California Medical Association initiated the first Blue Shield plan for payment to the doctors. Michigan Medical Service was the second pioneer, starting the next year. This has had a comparable growth. At first, Blue Shield was only for surgical fees in the hospitals. However, it has broadened its benefits, and today the Michigan Blue Shield is actively pioneering in the field of much more extensive benefits. This pioneering is being accompanied by a good deal of controversy both within and without the medical profession, and charges, counter-charges, factual information, and misinformation constitute a great current open debate.

Blue Cross plans, because of the increased prices of all services and personnel, and increased benefits, have had to raise their rates. This is the subject of another controversy. In New York State, the demand for a 40 per cent raise in rates resulted in Governor Harriman requesting $100,000 to study Blue Cross: its administration, its coverage, its abuses, any related factors contributing to the high cost of hospital care; its philosophy, any needed regulation by the state, and the character of its Board of Directors. In Michigan, in 1956, after one of the rate increases, Governor Williams appointed a commission to study and investigate Blue Cross. The University of Michigan is currently studying the whole problem of prepayment insurance with a grant of $300,000. Massachusetts, Pennsylvania and other states have similarly studied and taken seriously this contemporary development in health care.[6] When coverage of this nature involves a large proportion of the population, it approaches the character of public utility. In such matters, in the public's interest, there has always been and always will be regulation by the state.

After the popularity and the principles of prepayment had been established by Blue Cross, the commercial insurance companies entered the field, selling cash indemnity policies. This is usually a lump sum payment to the patient for sickness bills which he incurred, rather than direct payment to the hospital or to the doctor. These companies have recently featured certain deductible and co-insurance clauses.* Since 1950, the sale of indemnity policies has even surpassed Blue Cross. Commercial indemnity insurance now covers 73 million people for hospital care (although total paid benefits by this type of insurance are slightly less than Blue Cross).[20]

In 1956, voluntary insurance agencies paid 2.8 billion dollars for medical services; yet this represents only 19 per cent of the total expenditures for medical care, indicating the tremendous unmet demand for additional insurance coverage.[2]

The third type of voluntary prepayment agency is the so-called "independents," many of which offer comprehensive care. In general, the service is provided by groups of doctors, many of whom are on full salary. Comprehensive care includes hospital care and medical care for most illnesses in homes, offices and hospitals. These plans cover 80 per cent of the cost of care for all illnesses, usually excluding mental illness, tuberculosis, and dental care. About 3.5 million people in the United States received their medical care under

*Deductible—The patient pays certain initial costs of care. Co-insurance—The patient pays a percentage, usually 20 to 25 per cent of all costs.

this form at the end of 1950.[22] The best-known groups are H.I.P. in New York, Permanente in California, and Group Health Association in Washington, D.C. The prediction is that more such groups will form rather rapidly.

*The Plight of Hospitals.*—In 1925, only 10 per cent of the cost of hospitalization was paid for by insurance of one form or another. The remainder was met by the individual from his own resources. Ten years ago, insurance paid 25 per cent of hospital cost. Today it is 60 per cent. The prediction is that by 1975, 90 per cent of all private expenditures for hospital care will be paid for by some form of prepayment insurance.[7] It follows, then, that any financial trouble that the insurance plans fall into—such as over-utilization of beds, soaring rates, cancellation of policies because of long-time unemployment—will have an immediate and sizable effect on hospital income.

If Blue Cross becomes too expensive for the average wage-earner, what will happen to the average hospital?

*The Increased Public Interest in Medical Care.*—In 1932, the now-famous Committee on the Costs of Medical Care made its report.[3] There were two conclusions which have become historical: (1) Medical services should be furnished largely by organized groups, preferably organized around a hospital, and (2) costs of medical care should be placed on a group payment basis. Neither of these recommendations received much acceptance at that time.

In 1938, the Report of the Inter-departmental Committee to Coordinate Health and Welfare Activities came from Washington.[12] The committee was impressed, among other things, with the findings of the National Health Survey of 1935-36 that: One-third of the population, including persons with or without income, was receiving inadequate or no medical services; the increasing part which hospitals play, year after year, in health and sickness services; and "sickness is commonly the leading cause of social and economic insecurity."

In 1947-49, the National Labor Relations Board ruled that health insurance might properly be included in fringe benefits for labor. Since then, organized labor has become increasingly vocal in demanding more complete and adequate up-to-date care for the average working man and his family. These voices represent, with their families and dependents, 40 million people. ("The largest single body of consumers or recipients of medical care who are in a position to do anything about it.")[5]

The 54th Congress on Medical Education and Licensure Meeting in Chicago, in 1958,[15] emphasized the significance of many social trends to medical practice, thus: The rapid scientific and technologic changes in medicine in recent times, the growth of specialization, urbanization, upgrading of population education-wise and in sophistication, the increasing importance of the hospital as a center for medical care in the community, the need for more effective co-ordination and utilization of medical facilities and resources, and the advantages of group practice.

The meeting in Washington in June, 1958, of the National Conference on Labor Health Services[16] emphasized again the demand for better organization of doctors and their facilities in extending the availability of complete and adequate and up-to-date medical care at a cost which employed groups can afford. They are very critical of "free choic" pronouncements of medical societies.

Finally comes the 1958 Rockefeller Brothers Fund Report,[17] recommending "group practice affiiliated with a common hospital, essentially all costs prepaid, comprehensive in scope. . . . We believe that this group practice prepayment approach, although by no means suited to all communities, could be advantageously adopted by more communities. . . ."

Thus, after twenty-five years, the burden of the song is the same: Prepayment, comprehensive care, group practice.

In all of this development, one new note is being added. For the first time, the public (that is, our customers) are becoming critical about the inadequacies of medical care.

A basic question of policy is: Should prepayment plans be only collection and payment agencies, or should they have any responsibility for the adequacy of the medical care for which they pay? There is a growing feeling that prepayment agencies must assume responsibility to assure good quality of service.

"Illness and disability . . . are to an increasing extent becoming a matter of public concern," says Leonard Rosenfeld.[18] Mott states that the primary concern of any health plan should be the quality of medical care available to the subscribers.[13]

*Group Practice.*—A group practice may be composed of three or of 300 physicians. They may all be specialists; they may be a "diagnostic clinic," only; or more commonly, render treatment; or may dispense family care primarily by general practioners, aided by the needed specialists.

Payment may be made by the patient or by voluntary prepayment agencies, with partial or with comprehensive coverage or by combinations of these. Any metropolitan hospital partakes of the nature of a group, especially if there is a well developed residency training program and specialized staff. The general hospital has elevated the quality of medical care "by substituting organization for individualism in professional service without impairing professional individuality."[7] A hospital, by providing an office building for its staff, may start a group practice development. Other auspices may be a partnership, a non-profit organization, a university, or an industrial company (for its employes).

The milieu must be an atmosphere conducive to professional progress and harmony, and the patient must not be lost sight of "as a person." Granting this, doctors working together supplement one another's knowledge.† Consultation and referrals are simplified, for there is proximity and no money barrier. Experience, auxiliary staff and services, all facilities and other overhead items are more easily pooled, thereby service is rendered at less cost. The professional life may be more rewarding; provision can be made for staff review, research, study leave, retirement, and other perquisites.[5,21]

The growth of group practice *per se* has become more rapid since World War II. In 1951, there were 600 groups containing an estimated 6000 physicians. A current (August, 1958) estimate is 1000 groups with close to 9000 physicians.[4] Many leaders in American Medicine have played a significant role in developing the concept of group practice. The Mayos, Crile, Lahey, Ochsner, are merely names which are the best known. The advantages of group practice are becoming increasingly evident, not only to students of public health and medical economists, but to doctors both in and out of such groups.† A recent survey of group practices revealed that the motivation to join a group is frequently the opportunity to practice better medicine.[21] Many doctors in independent private practice will admit privately that there are many advantages to a group practice, even though they themselves would not want to join one.

*Free Choice.*—Naturally, in group practice there is not the free choice of every doctor's doorbell. There is the so-called "dual choice"; either the group or the individually practicing physician. However, there is a body of responsible opinion which maintains that the ancient and honored concept of "free choice of physicians" increases costs and is not appropriate to changes that are taking place in medicine and in the community, at large. George Baehr[1] said that laws guaranteeing everyone who has a medical license the right to practice medicine, surgery, and midwifery are not really in keeping with our present-day practices. Donald Munro[14] similarly has commented that free choice of physicians does not guarantee the best, or even adequate medical care. Munro urged an educational effort on the part of the New England Surgical Society to acquaint the public with such deficiencies, with the rights of the public for adequate care, and with the professional responsibilities to deliver that care.

Cruikshank[5] described the situation in medicine as comparable to the adjustment all must make from the simple agrarian society of fifty years ago to the complicated urban and industrial life today. The craftsman in the former era was responsible for making the entire product—for example, one entire wheel, of which he was justly proud. The mechanic of today is responsible for one small part in a large-scale organization. The doctor is caught in the same maelstrom. Cruikshank further states that solo practice, fee-for-service are of these older values and "the problem is how to develop arrangements under which the personal and social values that were associated with it can be preserved in the practice of modern Twentieth Century medicine." Baehr said practically the same thing: "Organization is an essential feature of American Industry, of Labor, and today, of modern medical services. The public needs to learn this truth."[1]

Studies by H.I.P. in New York have shown that when medical service was rendered by their groups,

†A recent item in the *Wall Street Journal* (June 30, 1958) commented on the increasing difficulties doctors are encountering in keeping abreast of 400 new drugs each year, digesting 6000 medical journals. "One group clinic assigned one of their members to read all of the drug advertising material which came to them. His loss was estimated at $50 per week for this time, 'but it was worth it.'"

annual hospital admissions per 1000 population were 18 per cent less than for Blue Shield subscribers and hospitalization days were much less (fifty-eight instead of sixty-eight days per 100 population per year.)[8] Also, perinatal mortality (defined as deaths between the twentieth week of gestation to one week after birth) was 30 per cent less than for comparable private patient deliveries in New York City.[10]

The United Mine Workers found that when they finally limited choice of physicians, their costs decreased, and the relative efficiency of medical care increased.[9]

Naturally, such trends towards abandonment of free choice have caused a reaction among segments of the medical profession, and in some places legal battles have developed. In Colorado, the State Medical Society had a bill introduced which would make it illegal to practice in a panel, defining a panel as a "list less than the total number of licensed physicians." Similar legislation was introduced in the Kentucky legislature. Both of these proposals failed to become law. The courts have held that such disciplinary measures are in restraint of trade, and violate the Sherman Anti-Trust laws exactly as a business combination might do. While the courts have ruled against corporate practice of medicine in which the services of hired doctors are sold for a profit, no court has applied the "Corporate Practice Rule" against a non-profit consumer-sponsored prepayment medical service corporation.[11]*

## Comments

It behooves us to take a mature and historic viewpoint of these matters which, at the present time, are being subjected to debates in almost every county medical society, of articles in any magazine one may pick up, of reports in the daily papers, and of serious studies in specialized technical journals.

Fifty years ago, the family doctor was able to give his patients all the care which was available at that time. The customer (again the prepayment customer of the future) is now lost in a maze of more than twenty specialists among whom he must often make his own selection. Some of these organizations buying medical services, with the large amounts of money involved, are critically surveying what they are getting for their money. Public health authorities, sociologists, students of economics are doing the same thing. They are studying the abuses of insurance. Some studies have shown that appendectomies have increased when there is Blue Cross or indemnity insurance coverage. There is growing evidence that there is unnecessary hospitalization under existing forms of medical practice.

There is no agreement today as to whether the purpose of voluntary health insurance is an anti-state medicine plan, a system of payment for certain costs of medical care, or a public health measure designed to provide comprehensive service.

Our thinking today must include all varieties of service available to the total community.† The adequacy of medical care will be critically surveyed by groups which heretofore have been considered our customers. We have dealt with them kindly, but our authority in the past was unquestioned. In the future we may have to deal with them as partners. Many studies indicate that the American public wants more complete coverage for illness and health care than the present plans afford.[10] They want to budget for illness as they do for their electric light or their rent. They want to write but one check each month, which would pay for hospital, ambulant care, diagnostic care, house calls, care for the chronically ill, care by specialists, by nurses, by dentists—all of the most modern up-to-date type. The psychology of prepayment of sickness bills will have to shift. The well person is not psychologically disturbed, anxious, in pain. He is not presented with a big doctor's or hospital bill which he did not foresee.[7] Well people, paying by the year, can make up their minds cooly, can be critical, can buy or bargain in large groups such as unions, church, farm social groups, civic or political bodies. These groups can evaluate what they are paying for and can obtain competent advice in doing so.

*The AMA, at the recent meeting in Atlantic City, attempted to redefine "free choice." "Those who receive medical care benefits as a result of collective bargaining should have the widest possible choice from among medical care plans for the provision of such care. . . . Each individual should be accorded the privilege to select and change his physician at will or select his preferred system of medical care, and the AMA vigorously supports the right of the individual to choose between these alternatives."

(Revised recommendation of the AMA Commission on Medical Care Plans approved by the House of Delegates, June 10, 1959.)

†A number of cities have instituted plans which the medical profession as well as the public should watch carefully and critically and objectively. Windsor Ontario Medical Service; H.I.P. in New York City; Group Health Co-operative of Puget Sound, are examples.

Whether we like it or not, 40 million customers may be demanding group practice from us or from the oncoming generation of physicians.

Rather than defend "free choice of physician" to the ultimate, shouldn't we re-examine the entire concept of free choice before getting into a fixed position?

## Conclusions

As a profession, we must recognize the following:

1. Vast social changes are taking place in our economy directly under our vision.

2. The kaleidoscopic advances in medicine, the impact and development of present-day specialization, the need for adequate care for all, present us with problems which the profession must share with the public at large.

3. All estimates indicate that there will be increasing demands for medical service, and there will be an increasing shortage of physicians. Medical care is highly prized. Whether total coverage on a community basis comes into vogue, or even if it does not, doctors and all those in medicine will always be relatively well paid.

4. Increasingly, our public wants nothing but the best. There will be increasing public concern and appraisal of the adequacy of medical care. The total costs of medical care must be reasonable. The economies in hospital utilization, diagnostic skills, group practice will be critically studied.

5. We must bear in mind that today, only about 20 per cent of the costs of illness is covered by insurance. Many feel that the extended Blue Cross coverage is adequate, yet benefits are increasing. Cash indemnity insurance proponents state that their coverage is more adequate because it is more flexible, and it may be sold more cheaply. Yet, are these adequate?

6. Our public, our customers, will increasingly be participants. They will not be sick and anxious people who function as an individual or family unit and cannot be bargainers about rates and charges. The public in the future may not allow the medical profession to decide these matters alone. The number of people and size of the organizations interested in better medical care who are not doctors may assure this.

7. It is in our interests, as well as in the interests of the community, that we as physicians familiarize ourselves with the various issues, identify the interests of the medical profession with those of the community, encourage and be prepared to examine any and all experiments in this field objectively.

There is more and more public criticism of the inflexible attitude of the medical profession. After the recent annual meeting in San Francisco of the American Medical Association, the *San Francisco Chronicle* (June 30, 1958) commented editorially that

> . . . The social viewpoint revealed by the AMA delegates was old-fashioned, stuffy, foundered under cliches. . . . In their resolutions on public affairs, the doctors fell miles behind other scientific professions. . . . The delegates seemed to be lobbying for the status-quo-ante-McKinley.

Out of these crosscurrents, conflicting views, and arguments, which are the present climate in the year 1958, will come an expanding body of experience upon which future change and better service will be based. These developments in public health, medical care plans, social welfare—call it what you will—are as vital and important as any scientific advancement in medicine. No thinking person will lightly dismiss these ideas and plans with a label of "socialized medicine," communism, or government control of the practice of medicine.

## References


1. Baehr, G.: The quality of medical service programs. *In* Papers and Proceedings of the National Conference on Labor Health Services, June 16-17, 1958. Washington, D. C.: American Labor Health Association, 1958.
2. Brewster, A. W.: Finances of Voluntary Health Insurance, 1956: Comparative Standing of the Nonprofit Plans and the Insurance Companies. Note No. 31. Washington, D. C.: Division of Program Research, Social Security Administration, September 11, 1957.
3. Committee on the Costs of Medical Care: Medical Care for the American People, Final Report of the Committee on the Costs of Medical Care. Publication No. 28. Chicago: University of Chicago Press, November, 1932.
4. Cooley, G. W.: Secretary, Council on Medical Service, American Medical Association (personal communication).
5. Cruikshank, N. H.: Labor's interest in medical care. New England J. Med., 257:866-870 (Oct. 31) 1957.
6. Davis, M. M.: Hearings foreshadow crisis for blue Cross. Mod. Hospital, 90:63-66 (April) 1958.
7. Davis, M. M.: Hospital income will come from everybody. Mod. Hospital, 90:51-54, 124-126 (Feb.) 1958; Service is the key to Blue Cross future. Ibid, 91:83 (Aug.) 1958.
8. Densen, P. M., Balamuth, E., and Shapiro, S.: Prepaid Medical Care and Hospital Utilization. Hospital Monograph Series No. 3. Chicago: American Hospital Association, 1958.
9. Draper, W. F.: Steps taken by the UMWA welfare and retirement fund to assure the quality of medical care. *In* Papers and Proceedings of the National

Conference on Labor Health Services, June 16-17, 1958. Washington, D. C.: American Labor Health Association, 1958.
10. Goldman, F.: Medical care for the American worker and his family. *In* Papers and Proceedings of the National Conference on Labor Health Services, June 16-17, 1958. Washington, D. C.: American Labor Health Association, 1958.
11. Hansen, H. R.: Legal background and problems. *In* Papers and Proceedings of the National Conference on Labor Health Services, June 16-17, 1958. Washington, D. C.: American Labor Health Association, 1958; Group health plans: A twenty-year legal review. Minnesota Law Review, 42:527 (March) 1958.
12. Interdepartmental Committee to Co-ordinate Health and Welfare Activities: Proceedings of the National Health Conference, July 19-20, 1938. Washington, D. C.: Government Printing Office, 1938.
13. Mott, F. D.: Community medical care programs. *In* Papers and Proceedings of the National Conference on Labor Health Services, June 16-17, 1958. Washington, D. C.: American Labor Health Association, 1958.
14. Munro, D.: On choosing a surgeon. New England J. Med., 258:74-77 (Jan. 9) 1958.
15. Papers Presented at the 54th Annual Congress on Medical Education and Licensure. J.A.M.A., 167: 21-57 (May 3); 167:182-214 (May 10) 1958.
16. Papers and Proceedings of the National Conference on Labor Health Services, June 16-17, 1958. Washington, D. C.: American Labor Health Association, 1958.
17. Rockefeller Brothers Fund: The Challenge to America: Its Economic and Social Aspects. Report of Panel IV of the Special Studies Project. Garden City, N. Y.: Doubleday, 1958.
18. Rosenfeld, L. S.: Trends in community health services. Speech presented before members of the house staff and the medical staff of Harper Hospital, Detroit, Community Health Association, May 24, 1958.
19. Shapiro, S., Weiner, L., and Densen, P. M.: Comparison of prematurity and perinatal mortality in a general population and in the population of a prepaid group practice, Medical Care Plan. Am. J. Pub. Health, 48:170-187 (Feb.) 1958.
20. Silverman, M.: The *Post* reports on health insurance. Sat. Eve. Post, 230:25-27, 127-128 (June 7); 230:36, 124-126 (June 14) 230:30, 100-102 (June 21) 1958.
21. Survey of Group Practice. J.A.M.A., 161:1391-1397 (Aug. 4) 1956. Survey of Group Practice, ibid, 164:1338-1348 (July 20) 1957.
22. U. S. Senate, Committee on Labor and Public Welfare, 82nd Congress, 1st Session: Health Insurance Plans in the United States. Report No. 359, Part 1. Washington, D. C.: Government Printing Office, 1951.

## CHANGING CONCEPTS IN THE TREATMENT OF ENDOMETRIOSIS

*(Continued from Page 105)*

endometriosis lesions left behind at hysterectomy (from bowel endometriomata to ovarian endometrial cysts) and these lesions atrophy with the ovaries left in place and functioning. Again, adapting the Meigs viewpoint, hysterectomy has deprived the endometrium of rhythmic changes. Significantly, Brakemann in 1924, performed a hysterectomy for an endometriosis of the bladder which required no further treatment. We have cured a case of endometriosis of the ureter by hysterectomy. It is readily seen that pregnancy, estrogen-induced "pregnancy equivalent," and hysterectomy have one thing in common: there is no cyclic withdrawal of progesterone. Although it is true that ovulation may occur after hysterectomy, certainly it is not regular and cyclic. The result is that aberrant endometrium doesn't proliferate and grow, but rather atrophies and becomes clinically insignificant.

*X-ray Therapy.*—The therapeutic recommendations —both medical and surgical—as outlined, are conservative and highly successful. However, as with any medical or surgical procedure, there are going to be some failures in attaining a desired result. For example, a rectosigmoid endometrioma might not respond to hysterectomy, or a pregnancy might not improve a cul-de-sac endometriosis. If this happens, and the patient is truly miserable with the disease, the patient may be castrated by irradiation. X-ray to the pelvis in a depth dose of 800 tissue roentgens will eliminate ovarian function thereby removing the stimulus to the aberrant endometrium. Knowing that we always have the radical plan of castration available, we apply the conservative measures with confidence. The need to castrate either by surgery or irradiation is *rare.*

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# Abruptio Placentae

## *A Survey of 131 Consecutive Cases*

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A SURVEY was conducted of all placental abruptions occurring in a five-year period (1953 to 1957) in a private 200 bed hospital. During this period there were 11,957 deliveries with 131 abruptions, an incidence of 1.09 per cent. This study included all cases of placental separation occurring between the twentieth week of pregnancy and the birth of the infant, as defined by Eastman.

Fetal mortality rate is dependent on a multitude of factors, the most important of which are: (1) severity of abruption, (2) delay in institution of therapy, (3) associated prematurity of the infant (which is commonly found), and (4) congenital defects.

Maternal mortality was formerly high, but improved methods of management have generally reduced it to 1 per cent or less. In this study there were no maternal deaths.

In general, the management of these patients was conducted by a conservative group of obstetricians and gynecologists. However, fetal distress was considered an indication for Cesarean section if the prognosis for vaginal delivery was not good. In this series, twenty-two Cesarean sections were performed for an incidence of 16.8 per cent (one was a repeat section). One classical section was performed, the remainder being low cervical sections. This is considerably higher than the incidence reported by Hester and Salley[4] of 3 per cent, but considerably less than Eastman's incidence of 37.7 per cent. Townsend[5] reported doing only eight sections in a group of 588 abruptions in Australia.

Hester and Salley[4] report a perinatal mortality of 68 per cent. Eastman[2] states the usual incidence will range between 30 and 60 per cent, depending on the definition of abruption used. Our incidence of perinatal mortality was 29 per cent. In this series there were twenty-three stillbirths and fifteen neonatal deaths. Of the fifteen neonatal deaths there were fourteen prematures, eight of whom weighed less than 2 pounds. The mortality figures include one stillborn with craniorhachischisis and one neonatal death with acrania.

Of these 131 patients only four had an associated maternal morbidity, while fifty required transfusions ranging from 1 to 7 pints. Two patients defibrinogenated in this series. After receiving multiple transfusions, Cesarean section was eventually performed with delivery of stillborn infants. One was a 20-year-old primiparous patient at 34 weeks gestation who developed a Couvelaire uterus and later a lower nephron syndrome (after receiving seven units of blood). The other, a gravida two, para one, developed a similar picture at thirty-two weeks gestation, received 6 units of blood and likewise had a Couvelaire uterus. Neither of these patients required hysterectomy. At the time of writing this paper, the second patient was in the hospital for a repeat section which resulted in the delivery of a healthy infant.

Greenhill[3] quotes figures for associated toxemia ranging from 42 to 69 per cent. It is of interest to note that in this study there were only five patients with an associated diagnosis of toxemia for an incidence of 3.8 per cent. There were no cases of eclampsia in this series. There were two sets of twins, one set delivered vaginally and the other by Cesarean section. Both sets survived.

In general the management of abruption at this hospital is as follows:

1. Typing and cross-matching of patient.
2. Replacement of blood loss.

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TABLE I. ANALYSIS OF ABRUPTIONS BY YEAR

| | 1953 | 1954 | 1955 | 1956 | 1957 | Total |
|---|---|---|---|---|---|---|
| Total abruptions | 25 | 30 | 20 | 29 | 27 | 131 |
| Private | 22 | 25 | 16 | 28 | 24 | 115 |
| Staff | 3 | 5 | 4 | 1 | 3 | 16 |
| Vaginal deliveries | 22 (88%) | 28 (93.3%) | 13 (65%) | 26 (89%) | 20 (74%) | 109 |
| Cesarean sections | 3 (12%) | 2 ( 6.6%) | 7 (35%) | 3 (11%) | 7 (26%) | 22 |
| Liveborn | 21 (80.7%)* | 27 (90%) | 17 (85%) | 23 (76.6%)* | 22 (81%) | 110 |
| Stillborn | 5 (19.3%) | 3 (10%) | 3 (15%) | 7 (23.3%) | 5 (19%) | 23 |
| Neonatal deaths | 2** | 4† | 2‡ | 3§ | 4° | 15 |
| Total perinatal mortality | 7 | 7 | 5 | 10 | 9 | 38 |
| Corrected death rate | 26% | 23.3% | 25% | 34% | 33.3% | 29% |
| Fetal loss from C-section | 1 | 1 | 1 | 1 | 3 | 7 |
| Fetal loss—vaginal delivery | 6 | 6 | 4 | 9 | 6 | 31 |
| Total deliveries | 2416 | 2439 | 2249 | 2486 | 2367 | 11,957 |
| Total liveborn | 2395 | 2419 | 2262 | 2476 | 2327 | 11,879 |
| Total stillborn | 33 | 26 | 27 | 46 | 43 | 175 |
| Incidence of abruption | 1.03% | 1.23% | 0.88% | 1.16% | 1.14% | (Av.) 1.09% |
| Incidence of stillborns from abruptions | 15.1% | 11.5% | 11.1% | 15.2% | 11.6% | (Av.) 12.9% |

*—One set twins.
**—Both weighed less than 2 lbs.
†—All weighed less than 4 lbs.
‡—Both weighed less than 4 lbs.; 1 with acrania.
§—Two weighed less than 2 lbs.
°—Three weighed less than 4 lbs.

3. Serial fibrinogen levels.

4. Artificial rupture of membranes.

5. Judicious use of I.V. Pitocin drip in selected patients.

6. Cesarean section for fetal indications when delivery from below is not possible, or for uncontrolled hemorrhage.

7. Antibiotics and general supportive measures.

Fibrinogen is available, but has not been used at this institution in the management of abruptions for reasons which will not be discussed at this time.

TABLE II. STATISTICAL SUMMARY, 1953 TO 1957

| | |
|---|---|
| Total live births | 11,879 |
| Total births and stillbirths | 12,054 |
| Neonatal deaths | 147 |
| Total stillborn | 175 |
| Total abruptions | 131 |
| Total patients delivered | 11,957 |
| Incidence of abruption | 1.09% |
| Total fetal loss | 38 |
| Stillborn | 23 |
| Neonatal death | 15* |
| Total perinatal mortality | 29% |
| Maternal mortality | 0 |
| Incidence of Cesarean section | 16.8% |
| Death from congenital anomalies | 2 |

*Fourteen prematures, 8 weighing less than 2 lbs.

## Summary

One hundred and thirty-one consecutive cases of abruptio placentae in a private hospital are presented. The total fetal loss in this series was 29 per cent and the Cesarean section rate was 16.8 per cent.

The indications for Cesarean section were fetal distress with vaginal delivery not possible, uncontrolled hemorrhage and previous section. There were no maternal deaths in this series.

Staff patients included in the above series are unwed mothers from the Florence Crittenton Home and constitute a normal socio-economic cross section of the population. The attending staff, whose patients constitute the majority of our cases in this series, serve as consultants on all staff patients, so that there is no difference in the general treatment of all patients in this study.

## References

1. Eastman, N. J.: Williams Obstetrics. 10th ed., p. 576. New York: Appleton-Century Crofts, 1950.
2. Eastman, N. J.: Williams Obstetrics. 11th ed., p. 627. New York: Appleton-Century Crofts, 1956.
3. Greenhill, J. P.: Obstetrics. 11th ed., p. 474. Philadelphia and London: W. B. Saunders Co., 1956.
4. Hester, L. L. and Salley, J.: The management of abruptio placentae. Am. J. Obst. & Gynec., 74: 1218, 1957.
5. Townsend, L.: Premature separation of the normally implanted placenta. Am. J. Obst. & Gynec., 10:534, 1957.

## HOW CHRONIC IS PULMONARY TUBERCULOSIS IN THE ELDERLY?

It has generally been thought that tuberculosis in older people is a very chronic disease, and that a complete x-ray survey of the elderly would be virtually sufficient to root out most of the disease in this group. Dr. Smith's study of pulmonary tuberculosis in people over fifty-five has shown that it is not uncommon for people in this age group to develop the disease in the same manner as a primary tuberculous lesion. He cited several instances where the older person contracted the disease as a result of infection from a younger member of the household.—JAMES SMITH, M.B., *British Medical Journal*, June 6, 1959.

# Wayne State University

## *Eighth Annual Symposium on Blood—January 16 and 17, 1959*

### PROCUREMENT, PROCESSING AND ADMINISTRATION OF HUMAN BONE MARROW FOR ATTEMPTS AT TRANSPLANTATION

EVALYN REPPLINGER, FARID HAURANI, ALBERTO CRISTOFANINI, EARL R. LONG, and LEANDRO M. TOCANTINS
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During the past few years much work has been done in bone marrow transplantation in animals. Earlier it was shown that animals can be protected against total body irradiation by injections of suitable marrow material. Subsequently it was found that murine leukemia could be controlled when the leukemic animals received total body irradiation followed by infusion of homologous marrow.

These experimental results in animals stimulated us to try and influence the course of acute leukemia and aplastic anemia in man. Bone marrow suspensions were prepared from excised ribs of healthy donors. A total of 2 to 18 billion marrow cells have been infused at one time without any immediate or remote reactions. Patients with aplastic anemia received no radiation, while those with acute leukemia received total body irradiation from 40-600 r. Both groups received steroids and other supportive therapy. One patient with acute leukemia received large doses of antimetabolites without x-ray treatment.

On the whole, the results were poor and there was no evidence of "take" of the infused bone marrow. However, there were some temporary improvements and, in one patient, there was a remission of seven months. The complications of total body irradiation as such, demand a great deal of attention and renders this mode of therapy a difficult one to handle.

This Symposium on Blood is being published also in *Thrombosis et Diathesis Haemorrhagica.*

CHAIRMAN
Walter H. Seegers, M.D.

### SOME BLEEDING DISORDERS RELATED TO PLATELET FACTOR 3

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A basic pattern in coagulation has been observed in bleeding disorders where platelet factor 3 is involved. In the thrombocytopenic state, 50,000 mm.$^3$ platelets or less, a poor prothrombin consumption time is observed in the absence of residual prothrombin in the serum. The short prothrombin consumption time is due to the formation, perhaps from prothrombin, of a platelet prothrombin-like factor, which is certainly similar chemically to prothrombin. This same pattern is present when platelet factor 3 is unavailable for blood clotting in congenital thrombocytopathy and the acquired thrombocytopathy of uremia, even though platelet numbers are normal. The defect in platelet factor 3 in each of these bleeding problems is vastly different both physiologically and morphologically in the face of this similar pattern. The authors believe this pattern is characteristic of all platelet factor 3 abnormalities.

### EXPERIMENTAL STUDIES WITH 5-HYDROXYTRYPTAMINE (SEROTONIN) AS A HEMOSTYPTIC AGENT FOLLOWING TRAUMATIC INJURY AFTER IRRADIATION IN WHITE RATS

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A decrease in the volume of blood lost as a consequence of traumatic injury during experimentally induced thrombocytopenic states (irradiation and antiplatelet serum) has been observed following intraperitoneal injections of 5-hydroxytryptamine. The procedure described by the authors (*Circulation Research* 6:456, 1958) was used to study blood loss in rats following lethal total body irradiation and in non-irradiated control rats.

The non-irradiated control rats bled a mean of 4.0 ml. Decreased bleeding was observed in the irradiated rats during the first four days after exposure to the effects of ionizing rays. The radiation injured animals bled one-half as much as the corresponding non-

irradiated controls. The classical bleeding syndrome associated with radiation sickness was observed on the seventh, eighth and ninth days post-irradiation, during which time the radiation injured rats lost a greater volume of blood when compared to non-irradiated control animals. This enhanced bleeding coincided with the drastic depletion of blood platelets in the peripheral blood.

5-HT in a dosage of 3 mg./kg. was found to be highly effective in controlling bleeding from traumatic injury following total body irradiation. For the first five days after irradiation, the response elicited by this compound in the irradiated rat was indistinguishable from the corresponding effect in the control animal, that is, 0.1 ml. blood. It may be of some interest to note that a diminished response to 5-HT was observed during the time of maximum thrombocytopenia suggesting that circulating blood platelets are essential in this interaction. Other amines (epinephrine and norepinephrine) associated with platelets did not decrease blood volume loss.

A decrease in mortality rate from hemorrhage associated with traumatic injury in post-irradiation states was observed after parenteral administration of 5-HT. All of the irradiated rats died as the result of the bleeding procedure which were bled on the days of maximum platelet deletion that did not receive 5-HT.

## PURIFICATION AND IDENTIFICATION OF PHOSPHOLIPIDES, WITH PROCOAGULANT ACTIVITY FROM BRAIN, PLATELETS AND SOYBEAN

H. Jensen, Donald G. Therriault and Thomas Nichols
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The term *procoagulant* is used for a phospholipide preparation which on interaction with certain clotting factors yields a prothrombin activator.

Utilizing fractional precipitation with organic solvents, countercurrent distribution and column chromatography, phosphatidyl serine and lecithin were obtained in chromatographically pure form from beef brain tissue. Measurements of the procoagulant activities of these phosphatides by determining their influence on the recalcification time and on the formation of thrombokinase in the thromboplastin generation test revealed that phosphatidyl serine or lecithin alone had only little or no procoagulant activity. However, when these phosphatides were allowed to react together in a chloroform solution, the reaction product, obtained after evaporation of the chloroform, was found to exert a very pronounced procoagulant activity.

Employing methods similar to those used in the study on brain tissue, comparatively pure preparations of the following phospholipides were obtained from beef platelets: phosphatidyl ethanolamine, phosphatidyl serine, lecithin and sphingomylin. The phosphatidyl serine content of bovine platelets seems to be relatively small. None of the four phospholipide preparations exhibited any appreciable procoagulant activity when tested alone. However, mixtures of phosphatidyl serine with either lecithin or sphingomylin or of phosphatidyl ethanolamine with either lecithin or sphingomylin showed pronounced procoagulant activity.

Apparently the procoagulant activity of soybean phosphatide fractions can be attributed mainly to phosphatidyl ethanolamine, since thus far no evidence for the presence of phosphatidyl serine has been obtained. Again it was found that the phosphatidyl ethanolamine alone showed no procoagulant activity, but following mixing with lecithin, procoagulant activity was generated.

These findings support the supposition that the presence of certain "procoagulant-active" phospholipides in the diet may conceivably contribute to hypercoagulability of blood and consequently to the development of atherosclerosis and possible coronary occlusion.

## PROPERTIES OF ANTI-PLASMA-THROMBOPLASTIN

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In continuation of former studies by E. Deutsch and H. Fuchs (VI Conf. Europ. Soc. Haemat., Copenhagen, 1957) we investigated the physical and chemical properties and the working mechanism of the anti-plasmathromboplastin. We found in the normal human serum two substances with anti-thromboplastic properties. Both migrate in the electrophoresis with the alpha-globulin fractions. We were able to separate these substances by different fractionations, such as ammonium sulfate fractionation, ethanol fractionation and changing the pH. They differ from each other in their heating stability, their storage stability, their adsorption on cation exchange resins, their dialysis properties, their curve of inactivation, and in their effect on dilution. Both need no calcium in the incubation mixture and their action seems to be stoechiometric.

## INTRACELLULAR DISTRIBUTION OF PROTHROMBIN REGENERATING CAPACITY

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That mitochondrial preparations have the ability to regenerate prothrombin activity from several different "inactive" prothrombin derivatives has been established. The major objective of the present study was to discover if the observed regenerating activity was limited to mitochondria or was distributed among other cellular fractions as well.

Cellular fractions of rat liver were prepared following the techniques of Schneider and Hageboom and adjusted to a 10 per cent solution with 0.25 M sucrose. Sub-fractions of mitochondria were obtained according to de Duve and associates. The substrate for the regeneration system was an "inactive" prothrombin derivative prepared with the use of liver mitochondria. For each cellular fraction conditions for maximal regeneration of prothrombin activity were determined. The regenerative capacity was not lost during prolonged freezing. Thrombin could not be detected as a by-product in either the inactivation or regeneration phase.

Measurements of specific activity (units of regenerated prothrombin/min./mg. protein) for each cell fraction were made to determine the intracellular distribution of the capacity to regenerate prothrombin at pH 7.8. This ability was concentrated within microsomes and light mitochondria. Microsomes were found to have four to five times and light mitochondria two to three times the capacity of either the total hemogenate or cytoplasmic extract.

Enhancement or inhibition of the regeneration reaction occurred when the cellular fractions were recombined in various ways. Augmentation of individual yields occurred when particulate fractions were combined in sub-optimal concentrations. However, the supernatant (soluble fraction) inhibited the regenerating capacity of the particulate fractions singly or combined.

Studies were also made with cellular fractions from the kidney, spleen and heart of the rat, as well as from organs of the rabbit. Cellular fractions from the liver and kidney were most active in the regeneration of prothrombin, but fractions from all organs exhibited some ability. Concentration of this capacity in the microsomes was clearly demonstrated.

## STUDIES OF THE EFFECT OF THOROTRAST ON BLOOD COAGULATION

TIBOR BODI, R. R. HOLBURN, J. GELDNER, R. T. CARROLL and L. M. TOCANTINS
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Prolongation of the venous blood clotting time after the injection of Thorotrast (thorium dioxide in 25 per cent dextrin) with 3.8 per cent sodium citrate has been observed in patients receiving the drug intra-arterially for cerebral angiography. A similar effect was observed in rabbits and dogs. The prolongation of the clotting time of whole blood and recalcified plasma appeared fifteen minutes after injection and persisted several hours. The platelet count of the patient was unaffected but the plasma prothrombin time was increased. Thromboplastin generation was also markedly decreased. Addition of protamine to the whole blood or plasma *in vitro* corrected the defect in clotting times. Allowing the blood or plasma to stand several hours before testing resulted in the gradual loss of hypocoagulability and ended in hypercoagulability. The *in vivo* studies suggest the release of an endogenous heparinoid substance as the cause of the coagulation defect. The injection of citrate alone into dogs did not produce a change in coagulation. *In vitro* the addition of Thorotrast in high concentrations to whole blood resulted in lengthened clotting times but was ineffective when added to plasma.

## THE PSYCHOLOGY OF SCIENCE

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> "There are more false facts current in the world than false theories."
>
> CULLEN
>
> "You can have neither a greater nor a less dominion than that over yourself."
>
> LEONARDO DA VINCI

By "psychology" I mean: my study of my mind's existence itself. By "science" I mean: my mind's self-activity systematically directed towards developing my potential manpower.

Every "system of scientific procedure" is an outgrowth of a "system of psychology," quite as every system of psychology is an outgrowth of life's "human system." An educator who appreciates the basic fact that his psychological orientation decides his educational orientation, finds it necessary to do some research upon the order of his mind. Regularly he discovers that he has obscured, almost to the vanishing point, these mind strengthening truths: (1) all of his "facts of life" are nothing but evidence of the *fact of his life*; (2) all of his scientific data are nothing but his own self data; (3) all of his research (learning) experience is nothing but his own self-activity furthering his own self-development; (4) all of his refinement of himself as a scientific instrument (means), has been at the expense of his appreciation of himself as an *end*; (5) all that *can* reveal his life as worth living, *is* the realization that it is his own; (6) all that *can* support disesteem for his life is his

(piling up) disregard for his experience as entirely self-experience; (7) all of the health benefit of his scientific effort is safeguarded, if he steadily heeds it as augmenting his (ever-increasing) estimate of his own worth; (8) all humanization of science (the countervailing force now needed to prevent scientific suicide) can derive only from the scientist's cultivating the self-insight enabling him to call his scientific soul his own; (9) all educational programs are decided ultimately by what the educator has been able to achieve of the insight: My mind consciousness decides the limits of my educational perspectives; (10) all that *can* be of any importance to anyone is himself, hence the advantage of growing to see one's world as one's own.

All knowledge obtained by careful inquiry, study and other experience, all systematized knowledge, all observation and classification of facts, all critical exhaustive investigation and experimentation, all principles and practices of exact scientific research—as well as whatever else is lived in the name of Science, needs must be lived in the name of the given scientist, for that scientist's healthy mental development to obtain.

I find psychotherapy (the process of appreciated self-discovery essential for wholesome self-esteem) to be the specific antidote for scientific training (and for all formal and informal education) based upon disregard for the inviolability of human individuality.

The urgent and constant health need of the scientist is to identify correctly all of his findings as "the business of living" his personal life. Laboratory work, experimental projects, scientific discoveries—all are wholesomely lived only as recognized and *appreciated* developments of *his* scientifically disciplined life. The scientist's discovery of the vastness of his world must spell out for him his own littleness, each of his scientific developments must dwarf his own recognition of his magnanimity, unless he develops the habit of mind of noticing that all of his life's experience (including his scientific research) consists of his self-knowledge and thus enhances his own worth.

Systematically observing myself as a fount of creative power, methodically studying my human being as a growing life which is everyday in the making, crediting myself with the realization that I have a truly marvelous mind which works scientific wonders for me—all such getting to work of this special part of my mind, this highest helpfulness which I call "self-consciousness," is a life-saving kind of accounting. It is this sense of selfness which puts value on life. And my possession of my life is my one and only true possession, my any other claim of property being a true illusion. "Anti" self-culture scientist, is contradiction in terms.

As Ruskin recorded, "there is no wealth but life." My only discovery worthy of the name is a growth of my mind, a new mental development. I can be sure of my ground really if I can recognize it as mind, otherwise not. My scientific research prospers when I can put to work the certainty of my conscious oneness of *my* world.

It is all which I cannot see as going on *within me*, which suffers me to live any of my scientific work as if it were not personally human. It is my scientific discipline which I can see as my inner workings, which commits me to a kind peaceful search for the attainment of human well-being, to a careful and caring observance of every law that concerns the furtherance of life.

My whole wisdom of life consists in my proper appreciation of LIFE as being that power which alone can make anything possible for me. What gives my presence of mind, my momentary self-awareness, an estimate of genuine solid worth, is my regard for myself as a growing life, as a developing human being, as a treasure of my self's experience. What every scientific meaning is in terms of my own mind's creating it—therein is its only truth (reality, scientific validity) to be found. The highest reach of human science is the clear scientific recognition of the scientist's psychological world. Otherwise must obtain the definition of the scientist as: one who knows more and more (of illusional externality) about less and less (of his own human development). "Learned ignorance," the consciousness of his ever-expanding room for his further human development, is the self-conscious scientist's reward for "hanging on" to his scientific self, for feeling equal to himself.

> "Read not to contradict and confute, nor to believe and take for granted—but to weigh and consider."
>
> FRANCIS BACON, 1620
> *Novum Organum*
>
> "Man one harmonious soul of many a soul
> Whose nature is its own divine control."
>
> SHELLEY

## OBSERVATIONS ON INTRAVASCULAR CLOTS

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Laki and Lorand (*Nature*, 166:694, 1950; *Science*, 108:280, 1948) observed that clots formed by the recalcification of plasma were insoluble in 5M urea, whereas clots formed by the conversion of purified fibrinogen with purified thrombin were soluble in 5M urea. In evaluating clots formed by the action of purified *Staphylococcus coagulase* on purified fibrinogen or plasma, it was found that such clots were

soluble in 5M urea. In view of the fact that clots from shed blood were insoluble it seems desirable to study the denaturation characteristics of fibrin clots from autopsy material.

Postmortem clots (chicken fat and red jelly clots) were uniformly soluble in the urea solutions. Evaluation of eleven cases of antemortem thrombosis in which three mural thrombi of the heart, one of the vena cava, one of the renal artery and six from the pulmonary veins were all partially soluble in 5M urea. The degree of solubility varied with the age of the clots and consequent degree of organization. Clots less than four days of age varied in solubility from 80 to 90 per cent.

Histologic observation of residues of clots after incubation in urea revealed cellular elements and small amounts of fibrin. One clot from a case of a ruptured liver following needle biopsy was evaluated for its solubility in 5M urea. This clot was not soluble in urea. In view of the fact that fibrin clots formed in the vessels and those formed outside the vessels have different chemical properties, that is, degree of solubility in 5M urea, it is reasonable to assume that they may have been formed by different mechanisms.

## THE NON-ENZYMATIC INDUCTION OF FIBRINOLYSIS

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The *in vivo* induction of mild degrees of fibrinolysis by non-enzymatic substances has been reported for several compounds with vasomotor activity. The intravenous administration of nicotinic acid in man has recently been found to result in fibrinolysis. (*Proc. Soc. Exper. Biol.*, 98:755, 1958). The phenomenon was not found to occur in dog, rabbit, rat, or guinea pig, nor does it result from the *in vitro* addition of nicotinic acid to human plasma. In spite of clear evidence of absorption in man, oral nicotinic acid fails to induce fibrinolysis. Only in one patient, a cirrhotic with a portocaval shunt, did oral nicotinic acid induce lysis, suggesting that initial circulation of all the administered nicotinic acid through the liver is incompatible with fibrinolysis activation. After single doses of nicotinic acid, oral or parenteral, the subject will not respond with lysis to subsequent parenteral doses for several hours or days. Continuous oral medication is followed by prolonged periods (weeks or months) of resistance to the usual lysis pattern of subsequently administered intravenous nicotinic acid.

Other flush producing and vasomotor drugs studied all failed to cause the clear fibrinolysis seen by "thrombelastograph" and test tube observation of plasma specimens after parenteral nicotinic acid. Nicotinamide also does not induce lysis, but does altar the usual lytic response of subsequent parenteral doses of nicotinic acid.

Removal of the clot of a post-nicotinic acid lytic specimen from its serum does not prevent its lysis, presumably because of adsorbed fibrinolysin. Normal clots added to the residual serum are less likely to dissolve than the native clot, although lysis of the normal clot has been clearly observed in some instances. Problems related to clinical application as well as theoretical explanation of the observed phenomena will be discussed.

## UROKINASE STUDIES

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Human urokinase is readily prepared by adsorption on porcelain. Pooled urine is filtered through a Coors filtering cylinder (porosity one). It is washed back first with water, eluting urine 'thromboplastin,' and then with 1/20 volume 1 M KSCN, eluting urokinase. The KSCN-solution is cleared by centrifugation, concentrated to 1/10 by evaporation with simultaneous dialysis, and finally lyophilized after further dialysis against distilled water. The yield of urokinase is 12-24 units (4-6 mg) per 1000 ml. urine. 1 ml. of pooled urine contains 0.025-0.05 units of urokinase. In this laboratory, one unit of human urokinase is defined as the amount, added before clotting, which is required to induce dissolution of one ml. of thrombin-clotted human ACD-plasma within 30 minutes at 37°C. Human urokinase incubated with human citrated plasma produces a progressive prolongation of the thrombin time, this is instantly normalized upon the addition of $CaCl_2$. Applied on human plasma plates, the urokinase makes it possible to test the effect of various substances on a homologous human fibrinolytic system. Thymol blue (20/ug./ml.), heparin (5/ug./ml.) and a protein free urine fraction consistently enhance fibrinolysis in this system. Urokinase-induced digestion areas on human plasma plates grow very rapidly for a few hours and then level off. Human urokinase excretion, measured quantitatively (K. N. von Kaulla, E. Schneeberger, M. Curry: *Fed. Proc.*, 17:167, 1958) in connection with cardiac surgery, reveal a decrease after the operation to a fraction of the preoperative values. The minimum excretion occurs on the third-fourth postoperative day; then, there is subsequent gradual return to preoperative values. In both surgical and medical patients, a sudden rise of urokinase excretion to a considerably greater level than precedent values can be, an indication of imminent bleeding.

These changes in the excretion rate are independent from creatinine excretion or specific gravity of the urine. Our previous studies indicated that some types of surgery and pyrogen-induced fibrinolysis in man can also increase urokinase excretion.

In the search for more satisfactory stimuli to induce fibrinolysis and the alteration of urokinase excretion in man, it was found that i.v. $CaCl_2$, Ronicol Compositum, and other drugs bring about a rather pronounced fibrinolytic reaction within minutes, depending on the injection speed. This finding warrants further extensive search for synthetic compounds inducing therapeutically useful fibrinolysis.

## PURIFICATION OF UROKINASE AND SOME CHARACTERISTICS OF THE PRODUCT

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Human urokinase has been brought to a high degree of purity by procedures involving its approximately 100-fold concentration by the foam technique (Celander, Langlinais, and Guest: *Arch Biochem. Biophys.*, 55:286, 1955), further purification by Chromatography on silicic acid (Ploug and Kjeldgaard: *Biochim. Biophys. Acta*, 24:278, 1957) followed by ammonium sulfate fractionation and separation from remaining impurities by means of chromatography on diethylaminoethyl (DEAE)-cellulose. The procedure is quantitative through the ammonium sulfate fractionation; the success of the second chromatographic step depends upon obtaining a satisfactory lot of DEAE-cellulose. The material so prepared has approximately 6,000 units urokinase (Celander, *et al, loc. cit.*) per milligram protein, corresponding to approximately 60,000 units per milligram protein when assayed by the method of Ploug and Kjeldgaard *(loc. cit.)*. From the data of the latter authors, the preparation appears to be nearly homogeneous. Under optimal conditions the overall yield approaches 100 per cent. Urokinase so derived has been used (1) in the study of profibrinolysin contamination in human fibrinogen prepared by the freeze-thaw technic with the resulting data indicating that about 0.03 per cent of the profibrinolysin present in human plasma is retained in the average freeze-thaw preparation of human fibrinogen; (2) in pyrogenic studies in which 0.36 mg. of the material, injected into the marginal ear vein of rabbits, produced a 1-2°C. temperature rise; and (3) in studies of antigenicity in guinea pigs and rabbits. In guinea pigs a total of 0.18 mg. urokinase injected in divided doses over a period of one month produced a degree of sensitization sufficient to cause acute anaphylaxis and death when the animal was challenged with 0.18 mg. of the same preparation or with urokinase prepared locally by the method of Ploug and Kjeldgaard. Urokinase, isolated from the urine of rabbits injected with human urokinase, produced similar anaphylaxis in sensitized guinea pigs. Although neither anaphylaxis nor a precipitin reaction was obtained with urokinase in presumably urokinase-sensitized rabbits, the serum globulin of these animals was more inhibitory to urokinase than was the globulin of normal animals. The significance of these findings is discussed.

## EPSILON AMINOCAPROIC ACID: AN INHIBITOR OF PLASMINOGEN ACTIVATION

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Numerous substances have been described as plasmin inhibitors, but only in a few cases, due to the ambiguity of the methods used, has distinction been drawn between inhibition of plasminogen activation and inhibition of plasmin action. ε-aminocaproic acid, a newly described "plasmin-inhibitor" (British Patent Office Specification No. 770, 693, 1957) has been investigated not only on account of the intrinsic interest attached to the compound itself, but also as a model substance suited to the development of adequate methodology for such studies. Systems were developed for the obtaining of kinetic data and testing was performed against the plasminogen activators, streptokinase, urokinase and fibrinokinase. The effect of ε-aminocaproic acid was also tested on the enzymes, trypsin and plasmin, which possess both proteolytic activity and plasminogen activator activity (plasmin acts by autocatalytic action). ε-aminocaproic acid competitively inhibited the activation of plasminogen by streptokinase, urokinase and probably fibrinokinase, but inhibited plasminogen activation by trypsin non-competitively. The results were similar whether the appropriate test system contained human plasminogen or bovine plasminogen. ε-aminocaproic acid in concentrations exceeding 0.06 M was a non-competitive inhibitor of the proteolytic activities shown by plasmin or trypsin, but in lower concentrations it enhanced the proteolytic action of plasmin. The results supported the concept that plasminogen activation may occur by two mechanisms yielding plasmins with similar biochemical activities, but of different molecular size (*J. Biol. Chem.*, 233:86, 1958). The inhibitory actions of ε-aminocaproic acid on plasminogen activation were demonstrable at much lower concentrations than were required for plasmin inhibi-

tion. Where, as in plasma, both activities may occur together, the ability of ε-aminocaproic acid to inhibit plasminogen activator at concentration insufficient to effect plasmin activity permits their separate effects to be distinguished.

## THROMBOLYTIC THERAPY IN PATIENTS SUFFERING FROM MYCOCARDIAL INFARCTION AND OTHER THROMBO-EMBOLIC STATES. A CONSIDERATION OF ITS PRODUCTION EFFECTS AND HAZARDS

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Thrombolysis, a term used to designate the lysis of thrombin or emboli, is mediated by a mechanism involving the absorption or diffusion of plasminogen activator to a thrombus, consequent activation of intrinsic thrombus plasminogen and resultant thrombolysis. The intravenous injection of a priming dose of streptokinase followed by the infusion of a suitable maintenance dose will produce, in man, a constant and high level of circulating plasminogen activator. Although plasma plasminogen and plasmin concentrations fall to undetectable levels, the plasma, by virtue of its plasminogen activator content, will lyse preformed isotopically labelled human plasma clots. The thrombolytic activity of the plasma measured under these test conditions, which approximate the experimental conditions *in vivo*, is of the order of 100-500 micrograms fibrin lysed/ml plasma/hour. Thrombolytic states of thirty or more hours duration have been induced, by means of this method, in fifty patients suffering from thrombo-embolic disease of whom twenty-four had early acute myocardial infarction. The induced thrombolytic state resulted in the production of a coagulation defect evinced by a rise in the one stage prothrombin time due partly to a fall in plasma accelerator globulin content but more importantly to the development of plasma antithrombin activity. This activity was thought to be caused by the presence of fibrinogen breakdown products and its appearance could in part be prevented by the administration of hydrocortisone. Clinically, there was evidence that in certain instances *in vivo* thrombolysis occurred as a consequence of the treatment and that therapy could be administered without deleterious consequence. Despite possible theoretical objections to its use in patients with myocardial infarction, eighteen of nineteen patients treated early survived for six or more months. It is emphasized that many problems remain for future solution.

## CALCIUM PHOSPHATE CHROMATOGRAPHY OF PARTIALLY PURIFIED BOVINE PROFIBRINOLYSIN (PLASMINOGEN) AND ANTIFIBRINOLYSIN (ANTIPLASMIN)

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A 3-fold purification of non-dialyzed bovine plasminogen (*Amer. J. Physiol.*, 191:505, 1957) was obtained by forty-fold dilution and adjustment of the pH to 5.3, the plasminogen being in the precipitate. A further five- to six-fold purification was obtained on a small scale by chromatography on columns of calcium phosphate gel (*Arch. Biochem. Biophys.*, 65:132, 1956). At pH 6.8 plasminogen is eluted in the sodium phosphate concentration range 0.05M-0.10M. This material appears to contain at least one major impurity and has a specific activity approximately equivalent to that of human plasminogen prepared by the method of Kline (*J. Biol. Chem.*, 204:949, 1953). After removal of plasminogen from bovine serum, antiplasmin was precipitated between 40 per cent and 60 per cent saturation with ammonium sulfate. The antiplasmin fraction was further purified by dialysis and precipitation at pH 5.0, the precipitate being discarded. The supernate had a specific activity about five times greater than the original serum. On small calcium phosphate columns, a further ten-fold increase in activity was obtained by elution of the supernate in the phosphate concentration range 0.003M to 0.005M at pH 6.8. The eluted antiplasmin was very unstable, and lost its activity in 3 hours at 5°C. Larger quantities of a more stable preparation, having a lower activity (seven-fold increase only) but higher yield, were prepared by continuously applying the antiplasmin supernate in 0.04M sodium phosphate to a column.

## PREVENTION AND PRODUCTION OF THROMBOSIS BY ALTERATIONS IN ELECTRIC ENVIRONMENT

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This study represents an investigation into the association between bio-electric alterations and intravascular thrombosis. An electrically positive environment, achieved by imposing a direct current in the range of 1 to 4 milliamperes across a segment of vein which had been occluded proximally, consistently resulted in the formation of an intravascular thrombus. Heparin uniformally protected against this electrically induced thrombus, while dicumarol had no effect. The heparin protection was to be expected since in-

jection of heparin markedly increased the electronegativity of flowing blood in respect to the adventitia of the blood vessel, concomitant with its increase of clotting time. The impostion of an electrically negative field to a blood vessel prevented or markedly diminished the formation of a chemically induced intravascular thrombus. A current ranging between one and four milliamperes was used to make a segment of the femoral vein electrically negative. The opposite femoral vein was used as a currentless control and 500 units of topical thrombin were injected to both femoral veins which had been occluded proximally. After thirty minutes the veins were opened. In all instances a large thrombus had formed in the control vein while half the veins which were protected with a negative current contained no thrombi. The remainder had minimal thrombi which was significantly smaller than their currentless control. The summation of these results suggests that an electric alteration is one of the common denominators for intravascular thromboses, which occur subsequent to a variety of blood vessel trauma and change in the constituents of blood.

## OBSERVATIONS ON THE BIOSYNTHESIS OF STAPHYLOCOAGULASE

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*Wayne State University College of Medicine, Detroit, Michigan*

The following relates to both the unique position staphylocoagulase occupies in the clotting of blood and to the close tie it bears the pathogenicity of *Staphylococcus aureus*.

This work was initiated in 1950 with the study of the relationship of coagulase to the blood clotting scheme as the objective. The development and use of a special growth medium made convenient for study a potent concentrate of coagulase. The medium, a dialysate of heart infusion broth, was separated from the coagulase by dialysis and the coagulase was concentrated by lyophilization. Coagulase could also be removed by Seitz filtration. These coagulase preparations had no effect on conversion of fibrinogen in the presence of prothrombin activators. These and other observations offered no definition for the mechanism of coagulase clotting.

A number of special media were tested for coagulase production capacity. Often, luxurious growth coexisted with suppression of coagulase production. The possibility that these media presented varying amounts of material(s) necessary for coagulase synthesis was investigated. Dr. Isabel I. Szeto and I gave characterization to the coagulase production capacity of the dialysate of heart infusion broth. In all tested cases the substance(s) behaved as could a peptide.

## THE AMINO ACID COMPOSITION OF THROMBIN PREPARATIONS

KENT D. MILLER, RAY K. BROWN, GERARDO CASILLAS and WALTER H. SEEGERS
*Division of Laboratories and Research, New York State Department of Health, New York, New York, and Wayne State University College of Medicine, Detroit, Michigan.*

Five bovine prothrombin preparations containing traces of accelerator globulin (*Record Chem. Prog.*, 13:143, 1952) were completely activated at optimum calcium concentration in the presence of an excess of sedimentable lung thromboplastin. After removing the thromboplastin by centrifuging, the thrombin was precipitated from 50 per cent cold acetone. Subsequently, the thrombin was separated by chromatography on the ion exchanger, IRC-50 (XE-64) as described by Rasmussen (*Biochem. et Biophys. Acta*, 14:567, 1954). The active protein was obtained from the chromatographic solvent, 0.3M phosphate buffer, pH 8.0, by the addition of 3 volumes of saturated ammonium sulfate in the cold. The precipitate was collected by centrifuging and reprecipitated three times with 50 per cent acetone after dissolving each precipitate in water. These final thrombin products were dried to constant weight *in vacuo* at 58°C. The nitrogen content was 16.3 per cent of the dry weight. Constant boiling HCl which had been twice distilled in an all glass system was added in the proportion of 1 ml. per 5 mg. of thrombin protein. The solutions were sealed under vacuum and digested at 110°C. for varying periods of from seventeen to seventy-two hours. Very little humin formation was demonstrable.

TABLE I. THE AMINO ACID COMPOSITION OF BOVINE THROMBIN

| Residue | μMaa / 100μMN | g. aa Residues / 100 g. Protein |
|---|---|---|
| ASP | 6.05 | 8.10 |
| THR | 2.99 | 3.52 |
| SER | 3.48 | 3.51 |
| GLU | 7.06 | 10.86 |
| PRO | 3.44 | 3.89 |
| GLY | 5.44 | 3.62 |
| ALA | 3.04 | 2.51 |
| CYS | 1.85 | 2.20 |
| VAL | 3.95 | 4.55 |
| MET | 1.06 | 1.61 |
| ILEU | 2.61 | 3.45 |
| LEU | 5.85 | 7.70 |
| TYR | 2.36 | 4.83 |
| PHE | 2.66 | 4.22 |
| GAL.$NH_2$(?) | .64 | 1.08 |
| LYS | 5.32 | 7.93 |
| HIS | 1.37 | 2.18 |
| $NH_3$ | 4.26 | — .05 |
| ARG | 4.87 | 8.83 |
| TRY* | 1.60 | 3.24 |
| Total | 94.17† | 87.88 |

*Spectrophotometric determination—this determination gave 4.98 for TYR.
† μM aa N recovered per 100μMN.

The hydrolyzates were dried *in vacuo*, the removal of HCl being insured by drying two subsequent aqueous solutions of the hydrolyzed materials *in vacuo*.

Amino acid composition of the hydrolyzates was determined by chromatography on Dowex 50-X4 by the procedure of Moore and Stein (*J. Biol. Chem.*, 211:893, 1954) employing an automatic, continuous-recording apparatus designed after Spackman, Moore and Stein (*Analyt. Chem.*, 30:1190, 1958). Tryptophane and tyrosine were determined by the spectrophotometric method of Holiday and Ogston (*Biochem. J.*, 32:466, 1938). No reducing sugar was detected on reacting the thrombin with anthrone in concentrated sulfuric acid. Corrections for loss of amino acids during hydrolysis are based on their loss from bovine pancreatic ribonuclease A hydrolyzed under identical conditions and include 7.5 per cent for serine, 4 per cent for threonine, 3 per cent for glutamic acid and 1.5 per cent for aspartic acid. The analytical results appearing in the table are from duplicate determinations of a single preparation but are in good agreement with the values for the other preparations analyzed.

The discrepancy between weight and nitrogen recovery remains a problem in considering this data. Sufficient quantities of thrombin were not available for ash determination. It is possible that the thrombin was prepared as the ammonium salt by the fractionation procedures outlined, thus yielding high ammonia figures. Prothrombin (*Arch. Biochem.*, 49:276, 1954) is relatively lower in lysine and higher in serine and alanine content than thrombin. The reducing sugar of the prothrombin apparently is a constituent of the non-thrombin fragment produced during prothrombin activation (*Fed. Proc.*, 17:276, 1958).

## METABOLISM OF ISOTOPICALLY LABELED SERUM ALBUMIN

S. Fleischer, H. Walter and F. Haurowitz

*Indiana University, Bloomington, Indiana*

Rabbits, guinea-pigs, rats and chickens were injected with amino acids containing $S^{35}$ or $C^{14}$. A few hours or one to two days later the animals were bled; their plasma proteins were isolated and coupled with traces of $I^{131}$. If the doubly labeled serum albumin was injected into animals of the same or another species, we found invariably that the protein-bound radioactivity of the $S^{35}$- or $C^{14}$-amino acids persisted much longer in the circulation than the activity of $I^{131}$. We attribute the observed difference in the fate of the two isotopes to breakdown of some of the serum albumin in the tissues, excretion of iodinated breakdown products and reutilization of the internally labeled amino acids for the synthesis of new organ proteins. (*J. Biol. Chem.*, 224:107, 1957).

Are the injected serum albumin molecules broken down randomly or are "old" molecules broken down first? To answer this question we injected one group of rats with serum albumin from rats killed eight hours after the injection of $S^{35}$-amino acids and another group with the serum albumin of rats killed four days after injection of $S^{35}$-amino acids. We found no significant difference between the half-lives of the young and the old serum albumin molecules (Science, 128:140, 1958). This indicates that the serum albumin molecules are broken down randomly and not in dependence of their age. In other experiments (unpublished) we have injected one group of adult rabbits with the $S^{35}$-serum albumin of adult rabbits, another group with the serum albumin of new-born rabbits. The half-life of the serum albumins of both groups was approximately 6.5 to 7.0 days. In some of these experiments the serum albumin had been prepared by salting-out with ammonium sulfate, in others by precipitation with TCA and extraction with acetone. No difference between the half-life of these two preparations was detected. We conclude from our experiments that the serum albumin of newborn rabbits is identical with that of adult rabbits and that its metabolism is not affected by treatment with TCA.

## BIOCHEMICAL AND PHYSICOCHEMICAL STUDIES OF HUMAN PLASMINOGEN

Werner Baumgarten and Rose B. Cole

*Merck Institute for Therapeutic Research, West Point, Pennsylvania*

Plasminogen isolated from human plasma possesses two enzymatic functions when activated with streptokinase, the proteolytic and the fibrinolytic (activator) component. Definite differentiation of these two entities has not been achieved, however, it has been established that at least their precursors, proenzyme and proactivator, prior to conversion with streptokinase possess different stabilities. Similar relationships have also been found in purification studies of crude plasminogen by modified Kline procedures and by subfractionation.

## THE COMPARISON OF THE HYDROLYSIS OF TOSYL-DL-ARGININE METHYLESTER BY THROMBIN AND TRYPSIN

M. Laskowski, Jr.

*Purdue University, Lafayette, Indiana*

Sherry and Troll (*J. Biol. Chem.*, 208, 95, 1954) have shown that thrombin hydrolyzes tosyl-L-Arginine methylester (L-TAMe), the best of known substrates for trypsin. Later studies by many workers have shown that while the thrombin specificity towards several substrates is very similar to that of

trypsin the activity towards most tryptic substrates is very weak—thus suggesting a higher degree of preferential specificity for thrombin.

Surprisingly both thrombin and trypsin hydrolyze DL-TAMe almost completely. However, of the two, thrombin appears to discriminate a good deal less between the L and D forms, that is, the ratio of $k_3L/k_3D$ is considerably greater for trypsin than for thrombin. Some implications of this result on preferential specificity of thrombin will be discussed.

## SOME ASPECTS OF THROMBOLYSIS IN MAN

A. J. JOHNSON, W. R. MCCARTY and W. S. TILLETT
*New York University-Bellevue College of Medicine, New York, New York*

Clinical studies of thrombolysis in man, utilizing streptokinase or streptokinase-plasmin for the therapy of intravascular thromboembolic disease, are complicated by: (a) variations in the natural course of disease, and (b) an anti-inflammatory effect that may follow clinical use of the enzymes.

In the present studies, experimental thrombi were induced in human volunteers. Twenty-four or forty-eight hours later, streptokinase (SK) was infused under controlled conditions to produce a proteolytic system, *in vivo*, consisting primarily of: (1) circulating SK-plasmin; (2) circulating free SK (or activator); or (3) plasmin plus free SK. The relative efficacy of each system was then tested for its ability to produce sustained lysis of the experimental thrombi.

Thirty-eight thrombi were induced by direct irritation of the intima with a dental broach or by chemical irritation with sodium morrhuate. The position and size of the clots were documented clinically and by venograms. No spontaneous lysis occurred in all (13) controls. In each instance, SK was infused systemically, into a contralateral extremity.

In order to produce fibrinolysis, an initial priming dose was given which was calculated to just neutralize the circulating antibody and inhibitor in each patient. Therefore, additional infused SK was free to produce active fibrinolysis. The additional SK was given in an amount appropriate for the production of one of the three proteolytic systems enumerated above.

The duration of the sustained SK infusion (about twenty-four hours), and the amount, were determined by following the various biochemical constituents of the fibrinolytic system in the patient's blood, and by clinical and x-ray appraisal of the experimentally induced clot. After clot lysis had occurred, reformation of the clot was prevented, in those patients with sufficient residual plasminogen, by prolonging the SK infusion for an additional 4-6 hours. These studies demonstrate *in vivo* that: (1) Circulating plasmin, without free SK, was ineffective in the production of sustained clot lysis; (2) Moderate or large amounts of circulating free SK, without plasmin, depleted the circulating plasminogen (and plasmin) so that there was insufficient substrate for consistent, sustained thrombolysis; (3) Small amounts of circulation plasmin *and* free SK produced consistent, reproducible, thrombolysis and prevented reformation of the clots in all eleven instances.

## A TIME LAPSE CINEMATOGRAPHIC STUDY OF CLOT RETRACTION

GIORGIO BALLERINI and WALTER H. SEEGERS
*Wayne State University College of Medicine, Detroit, Michigan*

The film portrays the process of clot retraction as observed in test tubes. The events of two hours duration are reduced to less than one minute. The influence of some of the more commonly known variables on clot retraction are included for education purposes alone. In addition some of the results of more recent investigations are included. The extent of retraction is dependent upon temperature, cell volume, pH, fibrinogen concentration, thrombin concentration, calcium ion concentration, and platelet concentration. Plasma contains dializable material concerned with clot retraction, and this includes glucose, phosphorus, and perhaps other substances. Plasma also contains one or more proteins of importance to clot retraction.

## EFFECTS OF HUMAN SALIVA ON BLOOD COAGULATION

D. H. KANG and P. H. LEE
*Yonsei University School of Medicine, Seoul, Korea*

Human saliva posseses an ability which accelerates the prothrombin time and coagulation time of rabbit, dog, and human.

The nature of accelerating factor is not fully understood, but the work on its purification is quite advanced. It is destroyed by strong alkali as well as strong acid, is unstable to heat above 50°C and insoluble in alcohol, acetone, and ether, indicating the probability of its being protein in nature.

It is also precipitated by a half saturated to a completely saturated ammonium sulfate solution, and it is non-dialysable.

Further study shows it is absorbed by barium sulfate, but not by other adsorbents such as barium carbonate and kaolin. Since it is adsorbed by barium sulfate, and eluated by 3.8 per cent sodium citrate, we were able to collect a relatively large quantity of it.

It's ability to cause a shortening of prothrombin time in either the one-stage or two-stage procedure and clotting time is probably due to its interrelation with thromboplastin.

# Nineteen Hundred and Sixty

With the closing of the old year and the beginning of the new, the world is passing through a very significant epoch. We are entering a new year and also a new decade. History has been teaching us that progress, new methods, and new materials are changing our mode of life and our outlook upon life. The 1950 decade—physically, economically, and in every other indication—has been one of tremendous progress. Medicine has been in the forefront.

In the decade just passed we have seen the introduction of new methods, new drugs, almost a complete new field of surgery and therewith new problems for the doctors and for the public.

We have developed the atom into a useful servant and have adapted it to our medical field in an astounding manner. When one looks over the ten-year period, heart surgery has practically been born during this decade, cranial surgery is very much advanced, and the antibiotics have not entirely, but almost, replaced mastoid surgery.

We have practically doubled the use of our hospitals. In many areas, new wards or isolation areas have been established at tremendous expense where the acutely and desperately ill medical or surgical patients can be kept under twenty-four-hour observation and immediate care of the nursing and medical staff. This has not only increased the cost of medical care but has increased the economic stress of paying for that care.

The public attitude as expressed by articles in the general magazines has undergone a tremendous change. *The Saturday Evening Post* has just concluded a series about what is happening to the family doctor; *Life* has published a series about modern medical problems; *Look* has also presented very illuminating studies; *McCall's* has had many on similar lines; *Ladies Home Journal* has entered the field of sex and family relations, and *Kiwanis Magazine* had a wonderful article about why some hospitals are losing money. Ten years ago, in November, 1949, we had an editorial entitled "Is Your Hospital Spreading Tuberculosis?" in which reference was made to the *Woman's Home Companion*. Editorials in December, 1949 were "Welfare State", "Police State", and "Compulsory Welfare Plans", and in January 1959, "Vicious Publicity" which was stimulated by *Harper's Magazine*.

In this new decade, it is fitting that we look forward. THE JOURNAL of the Michigan State Medical Society is appearing in a partially new dress. We have changed the type faces hoping to make it more legible, more attractive and pleasing to our readers. We are making other changes in an effort to make a more usable journal. The contents page has been reconstructed, and many of the materials and articles are being gathered under different headings. Our scientific papers will have a different title page.

During the year, the Michigan State Medical Society will move into its new home in East Lansing.



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## Politics

We are entering upon a new year in local and national political situations and the Federal government is passing through a presidential election year. All political parties will be seeking votes and making programs.

National legislation needs to be watched seriously. The Jenkins-Keogh-Simpson program which will allow self-employed persons—doctors, lawyers, dentists, architects, et cetera, to establish a retirement fund before taxation, rests in the Senate. It has passed the House. This is the opportune time to convince the senators that the enactment of this legislation is desired by the public, not as a favor but as justice to the self-employed. It should be passed.

The Forand Bill, which would place up to 15 million people under socialized medicine, again will be considered more intensely by the congress. We believe that our members all know that this bill makes hospitalization and surgical service available to every person who is a beneficiary of social security. If a person receives security benefits, he is eligible for medical and hospital service under this act. The medical profession is interested in all the above legislation.

Instead of the Forand Bill, the Social Security Act desperately needs an amendment permitting and encouraging our "senior citizens" to work. The Social Security benefits are grievously inadequate but if the beneficiary works more than a pitifully small stint, his benefits are cancelled. *This restriction against working should be completely removed.* The forced retirement from gainful activity by legislation has never had justification in practical fact.

## Michigan Economics

Michigan is in financial trouble. The situation and the analysis depends on whether you are a Democrat or a Republican. The two do not agree either as to the seriousness of the economic situation or the method of caring for it. All agree that the State of Michigan is slow in paying its bills.

The medical profession is a wise and well educated group, trained to analyze and diagnose. Whenever given an opportunity, our members should lend their advice to the solving of Michigan's problems.

Constructive, cohesive, building-up efforts are sorely needed. As a profession we have the ability—not to mention the historic and traditional background—attributed to the revered "family doctor."

Many of our doctors are now, and have been, serving their communities. Information about one of the new Councilors, Dr. R. J. Mason, Birmingham, calls attention to his serving on the United Fund. Another, Dr. O. B. McGillicuddy, served in Lansing, and recently headed a very successful campaign. Luther R. Leader, M.D., of Detroit, Chairman of the Relative Value Study Committee, for years has been on the Detroit area United Fund—Red Feather Board, and very active. His Board for several years has set unprecedented campaign records. Dr. B. M. Harris is a member of the State United Fund Board. In Battle Creek, Dr. E. F. Jones, M.D., is president and two other doctors of medicine serve on the board of the Battle Creek Area United Fund. We are sure a canvass would show many more giving their active aid in numerous public trusts.

## Hospitals

Hospitals in Michigan and throughout the United States are in serious trouble.

Almost all of them must take care of indigent, aged, relief and welfare patients, the blind, the handicapped, and others with utterly inadequate incomes. The great advances in services, equipment, and facilities of the hospital have caused a tremendous increase in the basic cost of operating hospitals. In almost every state there are provisions to pay for welfare patients, but in most of them the amount paid is never equal to the cost required for maintenance and operation of those hospitals.

This situation holds in Michigan. We had such a sample this past year when our Crippled Children's Commission was over one-half million dollars in arrears in paying for services at University Hospital which is not State supported, contrary to the opinion of most people.

By legislation, the state has placed an upper limit on the amount it will pay for services to these patients. That leaves nearly half of the bill unpaid. The State is in financial difficulties, but in the social welfare department and for crippled children, it should make payments adequate to cover hospital cost. The state is faced with a major readjustment. If it buys automobiles or other materials, it pays the charges; but in the area of medical and hospital services, it puts an upper inadequate limit upon its payment. In present readjustment, governmental planners must face facts, correct defects, and prepare to pay welfare and relief bills on a prompt and just basis.

# Elections

## William Amos Scott, M.D.

At the annual session in September 1959, William A. Scott, M.D., of Kalamazoo, was elected Councilor of the Fourth Councilor District to fill the unexpired term of Ralph W. Shook, M.D., who died August 9. This term expires in 1961.

Doctor Scott was born in Kalamazoo on November 23, 1904. He attended Kalamazoo College and the University of Michigan, receiving his medical degree in 1930. He took his psychiatric internship at Traverse City State Hospital in 1930-1931, Ypsilanti State Hospital in 1931-32, was assistant physician at Ypsilanti State Hospital from 1932 to 1937 and has been in private practice in Kalamazoo since that time. He is psychiatrist to Kalamazoo College and Western Michigan University. He was consultant to the surgeon general at Percy Jones General Hospital in Battle Creek.

From 1942 to 1944, he served with the AAF, officer in charge of professional services at Amarillo, AAF Regional Hospital. From 1944 to 1945 he served overseas in Alaska with the Eleventh Air Force Command.

Doctor Scott is a member of the Michigan State Medical Society, the American Medical Association, and Michigan Society for Mental Hygiene. He is also a member of the Kalamazoo Chamber of Commerce, the Galens, Alpha Kappa Kappa, the Kalamazoo Club, and the Park Club. His office is at Bronson Medical Center. He is married and has two children.

## Robert J. Mason, M.D.

Robert J. Mason, M.D., was selected by the House of Delegates at the annual session in September as Councilor for the Fifteenth Councilor District, to fill the unexpired term of D. Bruce Wiley, M.D., which expires in 1960. Doctor Wiley resigned to become Secretary of the Michigan State Medical Society. Doctor Mason was born February 5, 1905, at Salida, Colorado. He attended the University of Chicago getting his A.B. degree in 1925, and medical degree from Rush Medical College in 1929. He was intern and resident at Henry Ford Hospital in Detroit from 1929 to 1932 in pediatrics.

He has been practicing in Birmingham since 1932. He is a member of the Oakland County Medical Society. He served as commander, medical corps, United States Naval Reserve, 1942 to 1946. Member of the Birmingham Chamber of Commerce (Director and Past President). In 1949, he was Director of the Birmingham United Fund, member of City Planning Commission, Fellow of the American Academy of Pediatrics, member of the American Medical Association, Michigan State Medical Society, Detroit Pediatric Society (past-president), Chairman of the MSMS Pediatric Section in 1951, and of the Child Welfare Commission. He is married and has three children.

* * *

B. M. Harris, M.D., Ypsilanti, was re-elected Councilor of the Fourteenth District, and William Bromme, M.D., Detroit, was re-elected Councilor of the Eighteenth District.

# Michigan Medical Service President

G. Thomas McKean, M.D., of Detroit, was elected President of Michigan Medical Service. He was selected at the first meeting following the death of L. Fernald Foster, M.D., who had been serving for about three years.

On September 29, 1959, four new directors were elected to the Board of Michigan Medical Service by the members of the Corporation, meeting during the annual session of the MSMS. J. S. DeTar, M.D., who had previously served on the Michigan Medical Service Board was returned to that Directorship. Six members of the previous board were continued in office.

On October 7, 1959, the Board held its annual election. At this time, much discussion revolved about the office of president and the need for a full-time executive in this position. Pending decisions in this regard, election of a new president was deferred and Doctor McKean continues in the office.

Doctor McKean was born in Detroit in 1908, received his A.B. degree from the University of Michigan, and his M.D. from Harvard Medical School. Internship and residency training were at the Boston City Hospital and at University Hospital, Ann Arbor. He was licensed to practice in Michigan in 1936 and

was certified by the American Board of Internal Medicine in 1942. During World War II, he served with the 17th General Hospital in the Army Medical Corps. Doctor McKean is clinical associate professor of medicine at Wayne State University College of Medicine and attending consultant at Herman Keifer Hospital. He is a staff member of Harper and Receiving Hospitals, Detroit. He was Secretary of the Wayne County Medical Society in 1948-50.

In 1958-59, he was chairman of the medical section of the Michigan State Medical Society and from 1950 to 1956 served on the Michigan State Sanatorium Commission. He has been active on the Committee on Prepaid Medical Care Plans of MSMS. He is a member of the American Medical Association and the American College of Physicians, Wayne County Medical Society, Michigan State Medical Society, American Trudeau Society, Detroit Academy of Medicine, Detroit Surgical Association, Detroit Medical Club. He has also been a councilor of the Michigan State Medical Society since July, 1955, and has been a member of the Board of Michigan Medical Service since 1955.

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# EDITORIAL COMMENT

## For Medical Examiners

*Kalamazoo Gazette*, October 24, 1959

The case for replacement of coroners by medical examiners which Prosecuting Attorney Jacob A. Dalm, Jr., made before the Kalamazoo Academy of Medicine demands serious consideration both by the medical profession and by the Board of Supervisors.

Dalm asserted that what is needed is "a pathologist with medico-legal training and experience."

The matter is not, of course, a pressing one for Kalamazoo County. The local coroners, presently, are doctors.

But that might not always be the case. The office is elective, and no special requirements are set up.

As the prosecutor pointed out, while nineteen of the eighty-three counties in Michigan have medical examiners rather than coroners, fifty-seven of the other sixty-four have coroners who are laymen.

Few can doubt that under such circumstances, a layman coroner often may fail to discover any telltale signs of homicide, or that coroners' juries (also, almost invariably laymen) have little background for deciding upon their verdicts.

The coroner system, however well adapted to a more primitive society it may have been, has largely been outmoded by the progress of science.

The prosecutor emphasized that he was not criticizing the coroner system as it functions now in Kalamazoo County.

We should look ahead, however. Changing the system takes time. It requires a resolution by the Board of Supervisors putting the question on the ballot, and approval by vote of the people.

Fortunately, this county's situation is such that mature consideration by all, including the voters, can be had.

## Medical Care Appraisal Plan

*AMA Annals of Internal Medicine*, October, 1959

In 1956, a Committee of the American College of Physicians developed a plan by which the quality of practice of internal medicine in the hospitals of this country can be appraised.

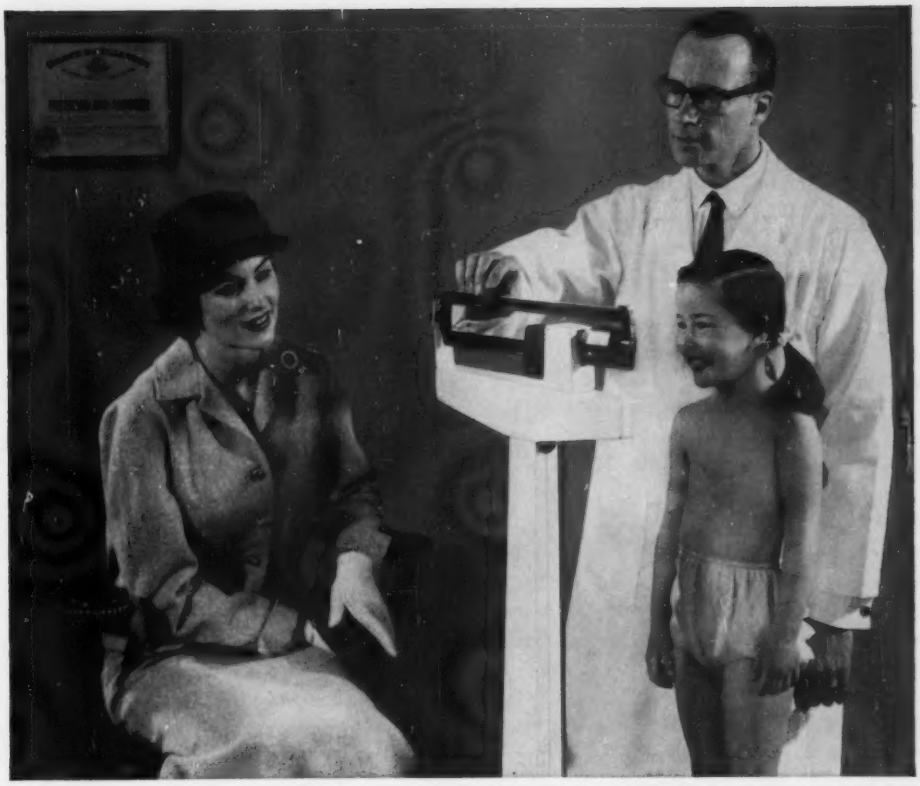
This study evaluated the quality of medical performance. It was made possible by an appropriation of $37,000 by the American College of Physicians and additional grants by the National Institutes of Health.

It was concluded that the quality of practice of internal medicine in hospitals can be judged by evaluating the records of a variety of patients by physicians who are trained as internists. The hospital staff has to assess the quality of its own work.

After three years of field work, a Medical Care Appraisal Plan was developed. This plan calls for the organization of an Appraisal Committee chosen from members of the hospital staff who practice general medicine or allied specialties. This Committee will evaluate medical care and act in an educational capacity only. Disciplinary action, if needed, would be left to the Executive Committee of the staff.

Medical records of patients treated, as well as those who have died, would be evaluated; the number of records examined being determined by the number of medical admissions each month. These should equal 20 per cent of such admissions. Records from different disease categories should be evaluated each month. Some records of every staff member who practices internal medicine should be examined at least once a year. A written report should be made for each record, but must *not* be kept with the patient's record. It should be available only to the Committee.

*(Turn to Page 134)*



# Underweight Children Gain and Retain Weight with Nilevar®

One of the most convincing evidences of the anabolic activity of Nilevar, brand of norethandrolone, has been its ability to improve appetite and increase weight in poorly nourished, underweight children.

A highly important feature of the weight gain thus produced is that it is not ordinarily manifested by deposition of fat but as muscle tissue resulting from the protein anabolism induced by Nilevar.

**Anorexia and "Weight Lag" Study**—Brown, Libo and Nussbaum have reported* consistent and definite increases in rate of weight gain in eighty-six patients, ranging in age from 7 weeks to 15½ years. This beneficial action of Nilevar was observed in the patients with organic and traumatic disorders as well as those whose only complaints were poor appetite and/or persistent failure to gain weight.

In this study, the weight gained was not lost after discontinuance of Nilevar therapy although many patients did not continue the sharp gains effected by the drug.

The authors are of the opinion that Nilevar is a highly useful anabolic agent for influencing weight gain in underweight children.

When Nilevar is administered to children a dose of 0.25 mg. per pound of body weight is recommended and continuous dosage for more than three months is not recommended.

Nilevar is supplied as tablets of 10 mg., drops of 0.25 mg. per drop and ampuls of 25 mg. in 1 cc. of sesame oil. Further dosage information in Searle Reference Manual No. 4.

G. D. Searle & Co., Chicago 80, Illinois.
Research in the Service of Medicine.

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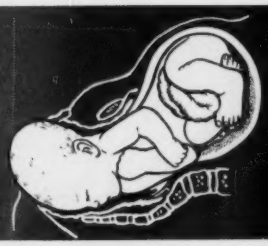
*Brown, S. S.; Libo, H. W., and Nussbaum, A. H.: Norethandrolone in the Successful Management of Anorexia and "Weight Lag" in Children, Scientific Exhibit presented at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 20-23, 1958.

# Obstetrical BREVETS



## *Perinatal Mortality*

The most dangerous experience in man's life, before he ultimately passes on, is being born. More people die aborning than between age one month and forty years. Hospitals and communities have accepted this high mortality as they accepted the high maternal mortality before 1930.

Perinatal loss is a problem that concerns the medical scientists, clinicians, public health workers; and through its impact on our socio-economic status, it becomes the concern of political scientists, nutritionists, economists and sociologists and the general public.

Public health agencies have played a pre-eminent role in the attack on the problem of perinatal loss. But there never will be a solution until the obstetrician, whether he be a general practitioner or a specialist, develops a permanent sustaining interest in the long range program of research, the basis of which is the perinatal mortality conference. At these hospital conferences all, or a selected group of foetal and neonatal deaths, are discussed by an inter-departmental group attended by obstetricians, pediatricians, pathologists and others interested in the problem.

A fringe benefit of the mortality study should reveal an improvement in morbidity, with the lessening of long range after effects of cerebral spastics, mental retardation and possibly congenital abnormalities.

Perinatal mortality studies are active in Saginaw, Detroit, Grand Rapids, and are being developed in other localities. We have all been interested for years in the near "obstetrical tragedy," and perinatal mortality studies help us to further evaluate these close calls. Dr. Toshach is too modest to mention his Michigan pioneer work in this field, but we of the maternal health committee are proud of his efforts and are vigorously supporting his original efforts.

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# Editorial Comment

*(Continued from Page 132)*

This plan is not intended to seek out instances of mismanagement, but rather to promote systematic investigations of hospital performance which will benefit every member. Suggestions of the committee would form the basis of general discussions at staff meetings and hence would encourage all members of the staff to assist in elevating standards.

Further information may be obtained from the national office of the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania.

## Farm Bureau Says Forand Bill Is "Socialized Medicine"

*Lapeer County Press*, September 10, 1959

A spokesman for the American Farm Bureau Federation last week rejected, as "an opening wedge to socialized medicine," proposals to increase the social security tax and provide payment of hospital and surgical costs for persons receiving social security benefits.

Keith Wallace, president of the Vermont State Farm Bureau, told a House Ways and Means Committee hearing that the Forand bill (H.R. 4700) would "very seriously impair, if not completely supersede," efforts to promote voluntary prepaid health and hospital insurance plans.

Mr. Wallace said the social security tax is "already a heavy burden" on farmers and other self-employed persons.

"The tax burden on the self-employed is not only greater than on the employed, but the responsibility for meeting such substantial payments accentuates for him the burden of the tax," he added.

"To further increase this burden by ⅜ of one per cent is undesirable, unneeded, and not requested by the people. It should not be imposed."

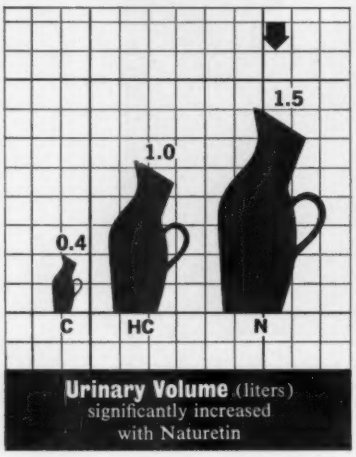
# more closely approaches the ideal diuretic

# Naturētin

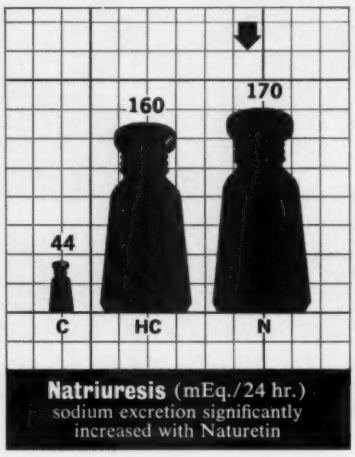
Squibb Benzydroflumethiazide

"When compared to other members of this heterocyclic group of compounds, this drug [NATURETIN] shows a significantly increased natriuresis and decreased loss of potassium and bicarbonate. In this respect it more closely approaches a natural or 'ideal diuretic.' It is effective upon continuous administration and causes no significant serum biochemical changes. It is effective in a wide variety of edematous and hypertensive states and represents a significant advance in diuretic therapy." *Ford, R.V.: Pharmacological observations on a more potent benzothiadiazine diuretic; accepted for publication by the American Heart Journal.*

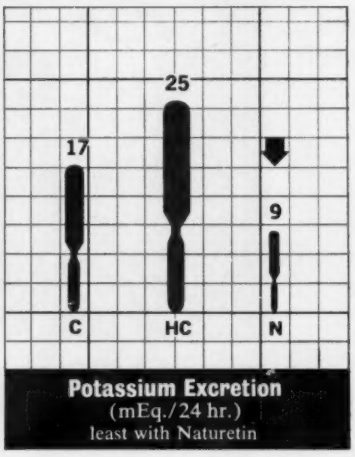
## Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin[1]



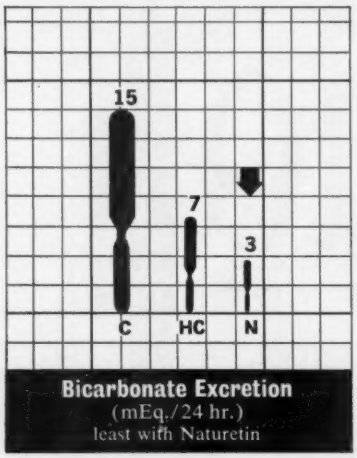

**Urinary Volume** (liters)
significantly increased
with Naturetin



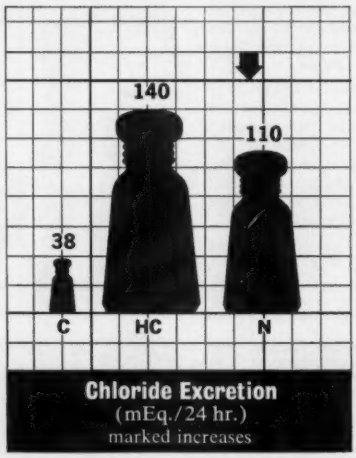

**Natriuresis** (mEq./24 hr.)
sodium excretion significantly
increased with Naturetin



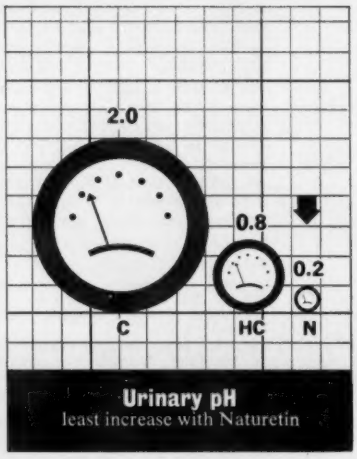

**Potassium Excretion**
(mEq./24 hr.)
least with Naturetin




**Bicarbonate Excretion**
(mEq./24 hr.)
least with Naturetin




**Chloride Excretion**
(mEq./24 hr.)
marked increases




**Urinary pH**
least increase with Naturetin

**Typical Doses: Chlorothiazide—1,000 mg.; Hydrochlorothiazide—50 mg.; Naturetin (Benzydroflumethiazide)—5 mg.**

*1. Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 1959.*

# A single 5 mg. tablet once a day provides all these advantages[2]

- prolonged action – in excess of 18 hours
- convenient once-a-day dosage
- low daily dosage – more economical for the patient
- no significant alteration in normal electrolyte excretion pattern
- repetitively effective as a diuretic and antihypertensive
- greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
- potency maintained with continued administration
- low toxicity – few side effects – low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other antihypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

[2]Reports (1959) to the Squibb Institute for Medical Research.

**Naturētin** – *Indications:* in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

*Contraindications:* none, except in complete renal shutdown.

*Precautions:* when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs—leg or abdominal cramps, pruritus, paresthesia, rash—suggestive of hypersensitivity, are noted.

**Naturētin** – *Dosage: in edema,* average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily or in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. *In hypertension:* suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

**Naturētin** – *Supplied:* tablets of 2.5 mg. and 5 mg. (scored).

SQUIBB

Squibb Quality—the Priceless Ingredient

Rx Naturetin 5mg. Disp. #30 Sig: 1 each morning.

'RAUDIXIN'® AND 'NATURETIN' ARE SQUIBB TRADEMARKS.

**AMA Washington Report**

# Social Security Expansion Looms as Election Issue

Congress embarked on a crucial election year session with expansion of the Social Security program shaping up as one of the major issues.

It was virtually a foregone conclusion that some liberalization of the program would be voted in the Democratic-controlled Congress, but the key question was how far the changes would go. In every Presidential election year during recent years, the House and Senate have approved a broadening of the program.

One of the prime reasons Social Security has been an election year "favorite" is that the program can be boosted without affecting the Federal budget. This is because it is financed through employer-employe contributions and is theoretically self-supporting.

* * *

OF SPECIAL INTEREST to physicians, of course, is the fate of the so-called Forand bill that would provide hospitalization, surgical services, and nursing home care for Social Security beneficiaries. This would be accomplished through even higher taxes on employes and employers than now scheduled through already-voted step increases.

Supporters of the controversial legislation—vigorously opposed by the Administration, the American Medical Association, and allied organizations—launched their move to win enactment this session.

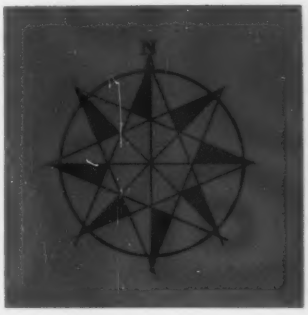
Sen. Pat McNamara, (D., Mich.), whose Senate Subcommittee on Aging held a series of hearings across the country during the recess, announced at the conclusion of the hearings that they showed a need for expanding Social Security to include health care for the aged. He indicated he thought the Forand bill did not go far enough.

* * *

A BATTERY OF SPEAKERS at a meeting here of the American Public Welfare Association also urged a sharp increase in benefits, with some advocating "cradle to grave" security for all.

Not all of the proposals for extending the program involved health care.

The Administration indicated it would recommend some expansion, especially in the disability program under which the Federal government helps the states provide assistance to persons over age fifty judged to be totally and permanently disabled. An influential lawmaker, Rep. Burr Harrison (D., Va.), disclosed that he would introduce legislation to remove the age fifty limitation to allow all persons regardless of age to participate. He estimated this would not require any hiking of the taxes. Rep. Harrison is Chairman of a House Ways and Means Subcommittee that held recess hearings on administration of the disability program.



Meanwhile, Chairman Wilbur Mills (D., Ark.) of the full Ways and Means Committee cleared the way for full-scale hearings this Congressional session on the entire issue of Social Security. In listing specific phases to be considered, however, the lawmaker did not mention the Forand proposal.

* * *

A SPOKESMAN for the American Medical Association told the Federal Communications Commission that the AMA believes the best solution to objectionable advertising and programs on television and radio is for the industry "to clean its own house."

Eugene F. Hoffman, M.D., co-chairman of the AMA's Physician's Advisory Committee on Television, Radio and Motion Pictures, declared "the medical profession stands ready to assist the networks and individual stations in determining accuracy and good taste of broadcast material involving health or medicine—either commercial or public service."

## Report of AMA House of Delegates

*December 1 to 4, 1959, Dallas, Texas*

### ACTION IN BRIEF

- Approved resolution stating: "Lest there be any misinterpretation, we state unequivocally that the AMA firmly subscribes to freedom of choice of physician and free competition among physicians as being prerequisites to optimal medical care. The benefits of any system which provides medical care must be judged on the degree to which it allows of, or abridges, such freedom of choice and such competition."
- Called upon each individual physician to wage "a vigorous, dynamic and uncompromising fight" against the Forand type of legislation.
- Reaffirmed previous policy statement approving in principle relative value studies by state medical societies.
- Urged state and local medical societies and individual physicians to implement the AMA program for recruitment of high-grade medical students.
- Urged medical schools to include course work in social, political and economic aspects of medicine.
- Reiterated the AMA's support of the Blue Shield concept.
- Urged Americans to get proper tetanus toxoid, original and booster, and other immunizations as indicated from their physicians.
- Suggested that AMA make available to school libraries information and literature showing the advantages of private medical care and the American free enterprise system.
- Approved creation of special study committee to evaluate present scholarship program and to investigate new aspects of programs to help meet the need for an increasing number of physicians in the future.
- Urged promotion of "Guides for Medical Care in Nursing Homes and Related Facilities."
- Reaffirmed the 1951 "Guides for Conduct of Physicians in Relationships with Institutions."
- Named Chesley M. Martin, Elgin, Okla., as "1959 General Practitioner of the Year."
- AMA President Louis M. Orr urged every physician "to take more active interest in politics, public affairs and community life."

## Professional Relations Conference Set for Blue Shield

The 1960 Blue Shield Professional Relations Conference will be held from February 1 to 3 at the Drake Hotel in Chicago, according to an announcement made today by Russell B. Carson, M.D., chairman of the Professional Relations Committee of the National Association of Blue Shield Plans.

A record attendance is anticipated for this 10th annual program, which brings together representatives of the medical profession and Blue Shield Plans for the specific purpose of discussing relationships between the Plans and physicians.

The 1960 conference theme is "Facing the Facts—in the Future of Blue Shield." Among the subjects to be discussed by recognized leaders in American medicine and Blue Shield are: "The Federal Legislative Climate and the Future of Voluntary Health Care Programs," "Blue Shield Coverage for the Aged," "Public Opinion and Its Application in Shaping Future Developments in Blue Shield," and "How Business Management Judges Health Care Coverage in Relation to Present Needs and Future Developments."

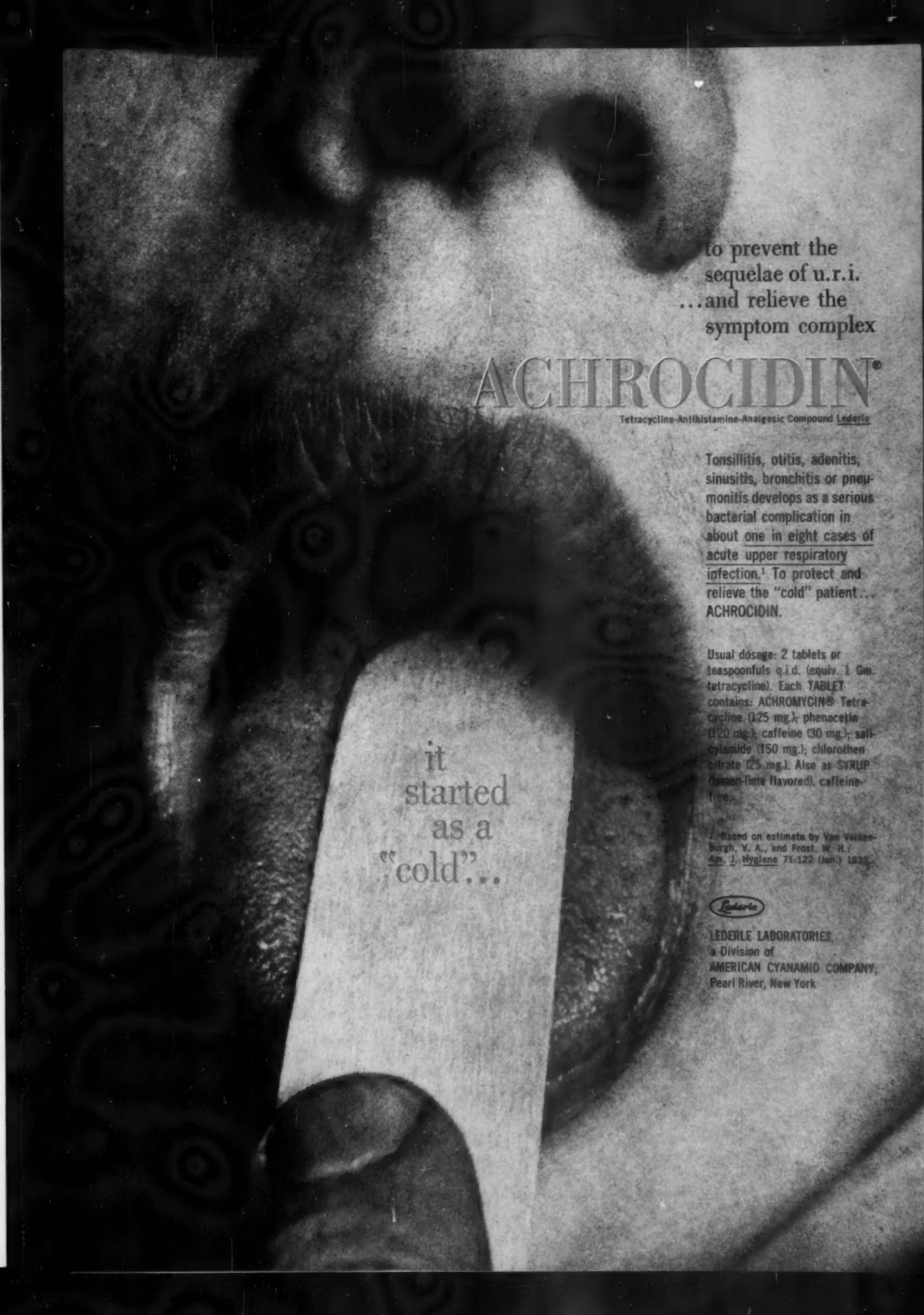
## Cancer Research Institute Directors Organize

Directors of cancer research institutes in America have formed the Association of Cancer Institute Directors for the purpose of exchanging information among the various institutes.

The first president is George Moore, M.D., director, Roswell Park Memorial Institute, Buffalo, New York.

The Association of Cancer Institute Directors has been designed to support investigations of the causes, nature, treatment and prevention of malignant diseases; to encourage the exchange of ideas, information, personnel and special facilities between groups with predominant interests in cancer; to foster educational opportunities in the bio-medical sciences; to provide guidance to private and civil organizations concerning cancer research, education and the care of cancer patients, and to expedite the dissemination of information by the meeting together of the scientific executive officers of cancer institutes.

Among the members of the Association is the Detroit Institute of Cancer Research.




to prevent the sequelae of u.r.i. ...and relieve the symptom complex

# ACHROCIDIN®

Tetracycline-Antihistamine-Analgesic Compound Lederle

Tonsillitis, otitis, adenitis, sinusitis, bronchitis or pneumonitis develops as a serious bacterial complication in about one in eight cases of acute upper respiratory infection.[1] To protect and relieve the "cold" patient... ACHROCIDIN.

Usual dosage: 2 tablets or teaspoonfuls q.i.d. (equiv. 1 Gm. tetracycline). Each TABLET contains: ACHROMYCIN® Tetracycline (125 mg.); phenacetin (120 mg.); caffeine (30 mg.); salicylamide (150 mg.); chlorothen citrate (25 mg.). Also as SYRUP (lemon-lime flavored), caffeine-free.

1. Based on estimate by Van Volkenburgh, V. A., and Frost, W. H.: Am. J. Hygiene 71:122 (Jan.) 1933.

Lederle

LEDERLE LABORATORIES,
a Division of
AMERICAN CYANAMID COMPANY,
Pearl River, New York

# Where a poly-unsaturated oil is called for in the diet, **Wesson** satisfies the most exacting requirements

*(—and the most exacting appetites).*


*Compared to other readily available vegetable oils, Wesson is unsurpassed as a serum cholesterol depressant.*

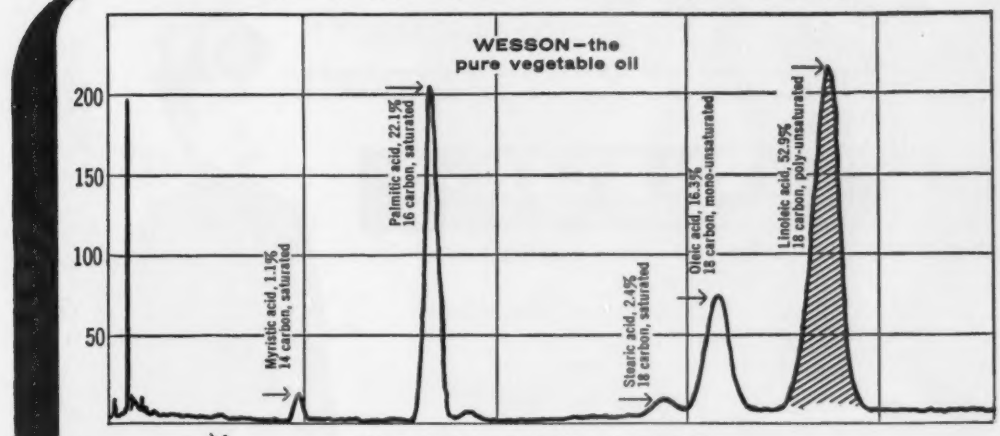
*Each pint of Wesson contains 437-524 Int. Units of Vitamin E*

**Faithful adherence to any diet** is much more likely when foods taste good. The preference for Wesson—amply confirmed by its sales leadership for 59 years—has been reconfirmed in recent tests with brand identification removed. Housewives in a national probability sample indicated marked preference for Wesson, particularly by the criteria of odor, flavor (blandness) and lightness of color.

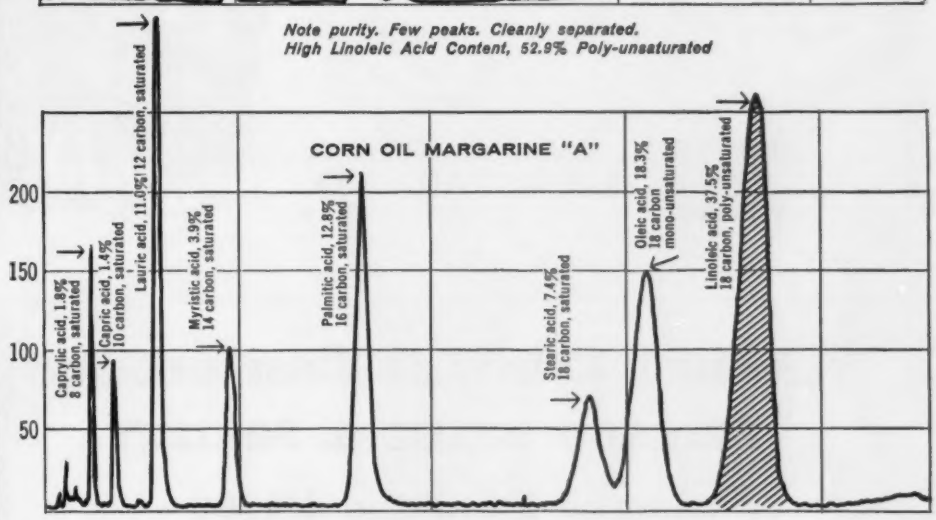
| **Wesson's Important Ingredients:** | |
|---|---|
| Linoleic acid glycerides | 50% to 55% |
| Phytosterol (predominantly beta sitosterol) | 0.4% to 0.7% |
| Total tocopherols | 0.09% to 0.12% |

*Never hydrogenated—completely salt free*

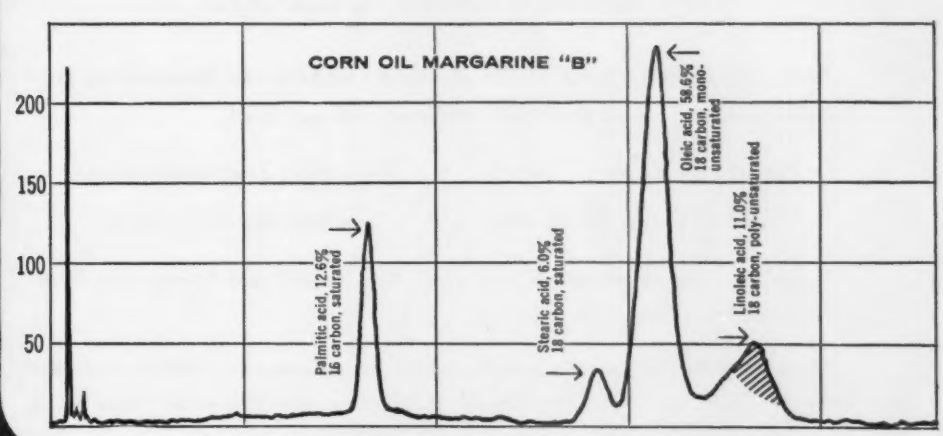
**GAS CHROMATOGRAPHS** *Produced by Independent Laboratory*




*Note purity. Few peaks. Cleanly separated.*
*High Linoleic Acid Content, 52.9% Poly-unsaturated*




*Note effect of coconut oil. Medium Linoleic Acid Content, 37.5%*




*Note effect of hydrogenation. Low Linoleic Acid Content, 11%*

# Synonyms for Pain Relief...

'TABLOID'
## 'EMPIRIN' COMPOUND®

Acetophenetidin ..... gr. 2½
Acetylsalicylic Acid .... gr. 3½
Caffeine ..... gr. ½

'TABLOID'
## 'EMPIRIN' COMPOUND® WITH CODEINE PHOSPHATE*

**No. 1**
Acetophenetidin ..... gr. 2½
Acetylsalicylic Acid .... gr. 3½
Caffeine ..... gr. ½
Codeine Phosphate .... gr. ⅛

**No. 2**
Acetophenetidin ..... gr. 2½
Acetylsalicylic Acid .... gr. 3½
Caffeine ..... gr. ½
Codeine Phosphate .... gr. ¼

**No. 3**
Acetophenetidin ..... gr. 2½
Acetylsalicylic Acid .... gr. 3½
Caffeine ..... gr. ½
Codeine Phosphate .... gr. ½

**No. 4**
Acetophenetidin ..... gr. 2½
Acetylsalicylic Acid .... gr. 3½
Caffeine ..... gr. ½
Codeine Phosphate .... gr. 1

*Subject to Federal Narcotic Regulations

**...providing the desired gradation of potencies for relief of varying intensities of pain**

IN
simple headache
rheumatic conditions
arthralgias
myalgias
common cold
toothache
earache
dysmenorrhea
neuralgia
minor trauma
tension headache
premenstrual tension
minor surgery
post-partum pain
trauma
organic disease
neoplasm
muscle spasm
colic
migraine
musculo-skeletal pains
postdental surgery
post-partum involution
fractures
synovitis/bursitis

relief of pain
of all degrees of
severity up to
that which
requires morphine

AND IN
fevers
dry,
unproductive coughs

**BURROUGHS WELLCOME & CO. (U.S.A.) INC.,** Tuckahoe, New York

*Your experience and trust throughout the years have established the wide use of the 'Empirin' family in medical practice—dependable analgesics for the effective relief of pain, fever, and cough—with safety.*


BURROUGHS WELLCOME & CO. (U.S.A.) INC.
Tuckahoe, New York

# Explains Medical Care Obligations

Professor B. James George, of the University of Michigan Law School, has issued a warning that parents who deliberately fail to authorize needed medical care for their children for religious reasons may be found guilty of manslaughter if the child dies.

"Parents are under a legal duty to provide food, clothing, shelter, and medical care for their children to the extent of their means and ability," he explains.

"This duty is imposed on parents without regard for their own personal beliefs. The state has an interest in seeing that at least minimum safeguards are taken for the health and welfare of minor children.

"Under the laws of most states, it's possible for a child to be made a ward of probate or juvenile court when his parents refuse to authorize needed medical care.

"Removed from his parents' physical and legal control, the child can then receive needed care and treatment under orders of the court. In this way, through expeditious legal proceedings, blood transfusions and other necessary procedures can be carried out and the child's life saved.

"This is the paramount interest, so far as the legal system is concerned."

Adults enjoy somewhat broader legal rights, the University of Michigan professor points out. When his refusal to accept medical treatment does not endanger the lives or well-being of others, the individual may decline any help. He is allowed to preserve his religious integrity, even at the risk of death.

Only when vaccinations or other types of treatment are imposed by law can the individual be compelled to accept them. The fact that some public official believes it is in the public interest to have everyone inoculated against polio, for instance, is not sufficient to force individual compliance to his commands, unless they are based on law.

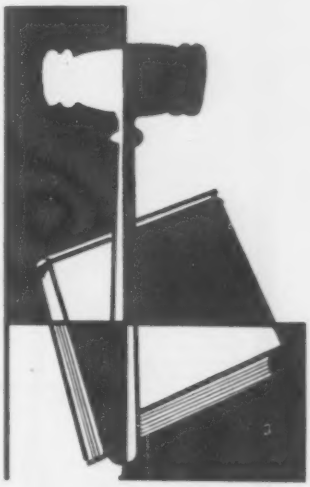
## Rule Premiums Deductible

Premiums paid for "package" health insurance are fully tax deductible. The Third Circuit Court of Appeals of the United States in a recent decision ruled that in the case of an insurance policy that provided both for reimbursement for medical expenses and for benefit payments for loss of income or loss of life resulting from accident or sickness, the premiums were fully tax deductible.

The revenue service and the tax court long have contended that under the tax law only premium payments which provide coverage for medical care may be deducted as a medical expense. Hence, they argued, for a policy combining coverage for loss of life or income with medical reimbursement, only that part of the premium attributable to the medical benefits qualified as a medical deduction.

The appeal court disagreed. It said Congress had not intended to draw so fine a distinction between amounts paid for various types of health and accident protection, but sought rather to permit a deduction for such coverage in full.

*—(Bulletin—Los Angeles County Medical Association)*



## Significant Tax Decision

U. S. Tax Court decision that a wife, though not a physician, may be recognized as a true partner in her husband's medical practice may find broad application. Cases are tried and decided on their merits, and the outcome of this one (Nichols vs. Internal Revenue) does not automatically extend this tax-advantage privilege to every such couple. But in cases where the wife is as essential to her husband's practice as was Mrs. Beulah Nichols, probability of these couples' qualifying for similar tax treatment would seem to be great, judging by crispness of this decision.

Following dissolution of a partnership with other radiologists in Seattle, Dr. Harold E. Nichols took his wife as a partner in April, 1953, with the approval of his accountant. Mrs. Nichols often worked seven days a week, handling billings, purchasing supplies, paying the bills, checking clinical reports and taking x-ray films home for her husband to read after illness in late 1953 curtailed his activities.

Dr. Nichols died in May, 1954. Internal Revenue Service subsequently held the partnership "a sham and invalid" in finding an income tax deficiency of $24,618 for the calendar year 1953. This decision was appealed by the widow, and the tax court has now held in her favor.

## Autopsy Limitation

Dear Doctor:

I have your letter inquiring as to the permissible scope of a validly authorized post mortem examination.

I find no statutory provisions or adjudicated cases in Michigan which place any specific restrictions on the scope of an authorized autopsy.

It is my opinion, therefore, that in the absence of any specific restriction in the consent or permit, the physician performing the autopsy is authorized to conduct it in the usual and approved manner practised by the profession and to remove for examination and study such parts of the body as must be examined and studied in order to accomplish the purpose of the examination.

In short, if the consent or permit is without restriction as to the scope of the examination, I believe it is sufficient to authorize examination of the brain if such examination is consistent with the purpose of conducting the autopsy. If, of course, the examination of the brain is not consistent with the purpose for which the autopsy is being done or if the consent to autopsy specifically restricts its scope, such examination should not be done without specific consent.

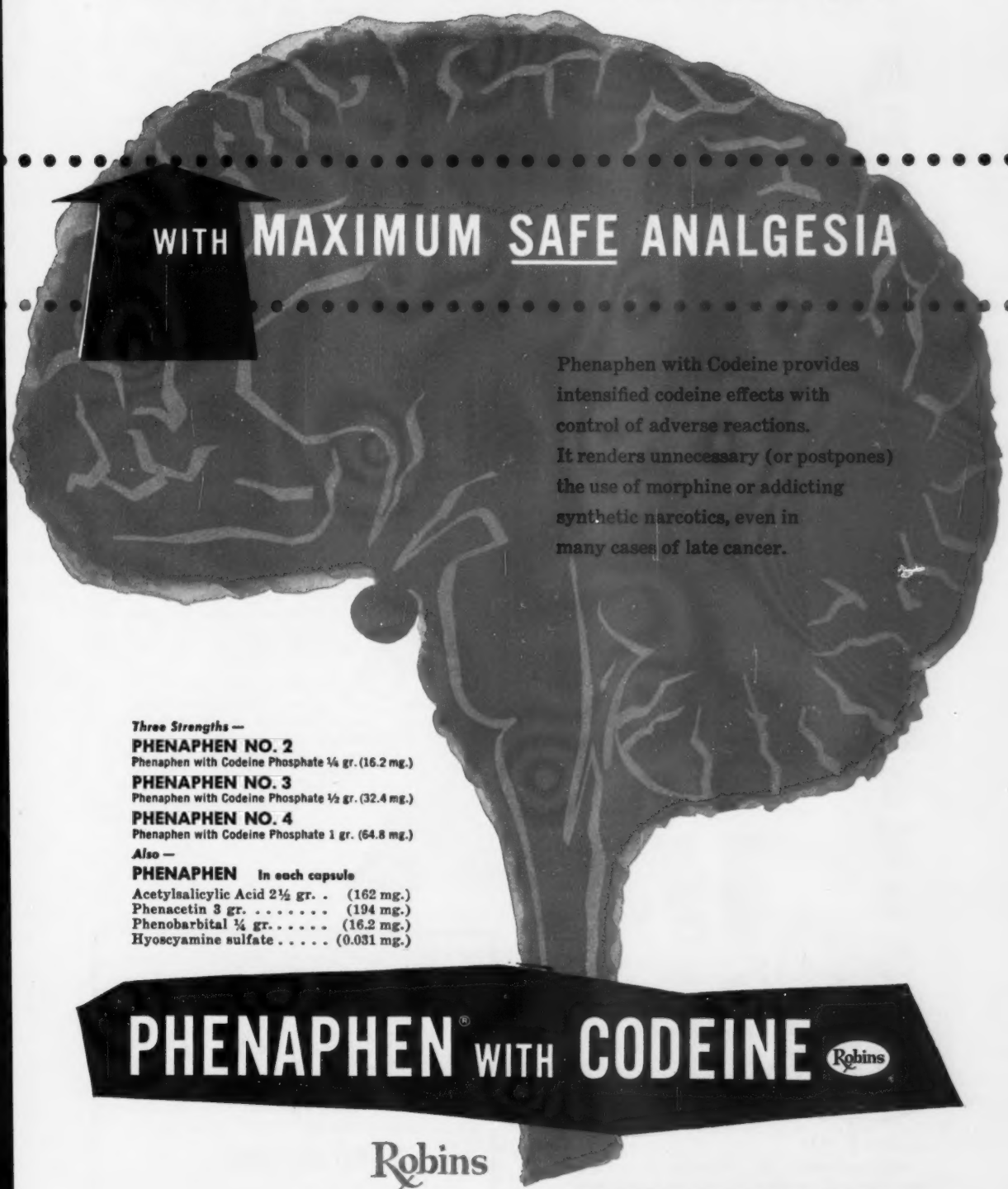
It must always be kept in mind that the person who has the right to authorize a post mortem examination has the right to impose the limits within which it is performed, and if such limitations are imposed in the consent, such limitations must be observed.

I trust that the foregoing satisfactorily answers your inquiry.

Very truly yours,
LESTER P. DODD
*Legal Counsel*

*(Turn to Page 150)*

# Raise the Pain Threshold



## WITH MAXIMUM SAFE ANALGESIA

Phenaphen with Codeine provides intensified codeine effects with control of adverse reactions. It renders unnecessary (or postpones) the use of morphine or addicting synthetic narcotics, even in many cases of late cancer.

*Three Strengths —*

**PHENAPHEN NO. 2**
Phenaphen with Codeine Phosphate ¼ gr. (16.2 mg.)

**PHENAPHEN NO. 3**
Phenaphen with Codeine Phosphate ½ gr. (32.4 mg.)

**PHENAPHEN NO. 4**
Phenaphen with Codeine Phosphate 1 gr. (64.8 mg.)

*Also —*

**PHENAPHEN** In each capsule

Acetylsalicylic Acid 2½ gr. . (162 mg.)
Phenacetin 3 gr. . . . . (194 mg.)
Phenobarbital ¼ gr. . . . . (16.2 mg.)
Hyoscyamine sulfate . . . . . (0.031 mg.)

## PHENAPHEN® WITH CODEINE

Robins

A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA

*Ethical Pharmaceuticals of Merit since 1878*

*(Continued from Page 148)*

## Rescission of Surgical Privilege

Dear Doctor:

I have your inquiry regarding the law in relation to actions for damages for slander or defamation in cases of rescission of surgical privileges in an accredited hospital.

Generally speaking, the elements of an action for defamation, which includes slander and libel, are (a) that the defendant has published or communicated to others statements which are false, (b) or of a defamatory nature, and (c) as to which no legal privilege existed. Generally, the truth of a claimed defamatory statement is a complete defense.

Applying these general principles to the situation arising from the recission of a doctor's surgical privileges, the first test would be to ascertain whether or not any statements were made, recorded or published which could be said to be defamatory. If not, it is difficult to see how any action could arise. If, in the handling of such a matter, any defamatory statements were made or necessarily implied, it would be necessary to test them both as to truth and good faith. If true, and made in good faith, it would seem that no action would arise.

There is also, I think, some degree of qualified privilege present in such a matter assuming, of course, that the rules, regulations and by-laws of the hospital and staff were strictly followed in whatever proceedings were taken. I think this latter is important both in relation to a possible action for defamation and as bearing on any right of action which the physician might have to reinstate his privileges. In short, if the rules, regulations and by-laws of the hospital and staff are followed strictly and if the action taken is in good faith and is not tinctured by personal considerations or other outside influences, no legitimate cause of action could be expected to occur.

There are no statutory provisions in Michigan bearing on this subject nor, so far as I have been able to learn, any adjudicated cases in Michigan on the subject. Cases embodying these principles have occurred in other states, however, and I believe the foregoing is in accord with the general weight of authority.

Sincerely yours,
LESTER P. DODD
*Legal Counsel*

*1601 Dime Building*
*Detroit 26, Michigan*

## The clock strikes 2—
## and your ulcer patient sleeps undisturbed

**ONE 10 MG. DARICON TABLET AT BEDTIME...**
controls hypersecretion, hypermotility, and spasm all night long. The sustained anticholinergic efficacy of DARICON is inherent in its structure and does not depend on special coatings.

**ONE 10 MG. DARICON TABLET BEFORE BREAKFAST...**
provides dependable relief for at least 12 more hours. In a large series of patients with peptic ulcer and other gastrointestinal disorders—some notably refractory to therapy—8 out of 10 responded to DARICON.

**DARICON®**
oxyphencyclimine hydrochloride

**B. I. D. DOSAGE**

**For 'round-the-clock relief of ulcer and other gastrointestinal disorders**

*A Professional Information Booklet is available on request from the Medical Department.*

Pfizer *Science for the world's well-being™* PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc., Brooklyn 6, New York*

*for the tense and nervous patient*

## relief comes fast and comfortably

–does not produce autonomic side reactions
–does not impair mental efficiency, motor control, or normal behavior.

*Usual Dosage:* One or two 400 mg. tablets t.i.d.

*Supplied:* 400 mg. scored tablets, 200 mg. sugar-coated tablets or as MEPROTABS*—400 mg. *unmarked*, coated tablets.

# Miltown®

meprobamate (Wallace)

WALLACE LABORATORIES / *New Brunswick, N. J.*

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**NOW**

*. . . a new way to relieve pain and stiffness in muscles and joints*

*indicated in:*

MUSCLE STIFFNESS

LUMBOSACRAL STRAIN

SACROILIAC STRAIN

WHIPLASH INJURY

BURSITIS

SPRAINS

TENOSYNOVITIS

FIBROSITIS

FIBROMYOSITIS

LOW BACK PAIN

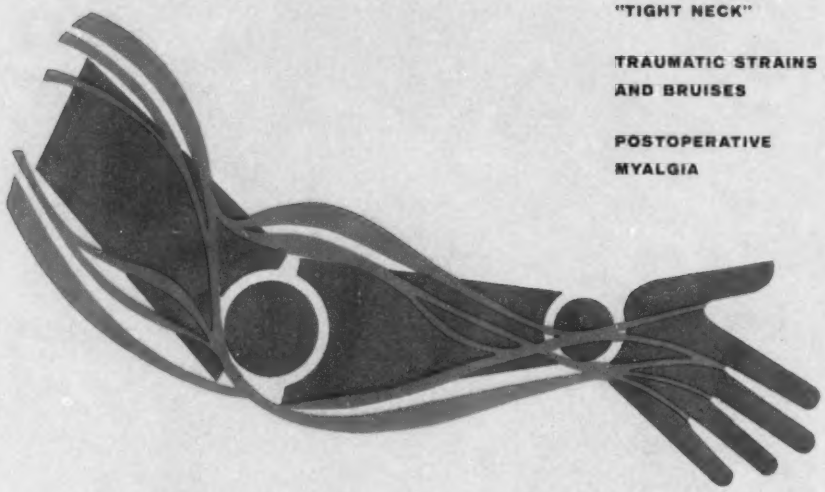
DISC SYNDROME

SPRAINED BACK

"TIGHT NECK"

TRAUMATIC STRAINS AND BRUISES

POSTOPERATIVE MYALGIA



■ Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain ■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

# SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids

■ More effective than muscle relaxants

**SOMA** has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with previously used analgesic, sedative or relaxant drugs.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

**ACTS FAST.** Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

**NOTABLY SAFE.** Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy, particularly on high dosage.

**EASY TO USE.** Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

**SUPPLIED:** Bottles of 50 white coated 350 mg. tablets.
*Literature and samples on request.*

WALLACE LABORATORIES, NEW BRUNSWICK, N. J.

## Offers 103 Scholarships

**THE NATIONAL FOUNDATION.**—Health Scholarship Program, now entering its second year, will offer 103 health scholarships for four years of study at fully-accredited schools of medicine. To be eligible, a student must be currently enrolled as an undergraduate at an accredited college and must be accepted for admission to medical school for the fall of 1960 by the applications deadline of April 1, 1960. The only obligation of Health Scholarship winners is to have the intention of completing their education and of serving the health field as a member of their chosen profession.

Information about the program may be obtained from the National Foundation Health Scholarships, 800 Second Avenue, New York 17, New York.

**MEDICAL PSYCHOLOGY.**—Monsignor Arthur F. Bukowski, president of Aquinas College, Grand Rapids, announces that John Ignatius Nurnberger, M.D., of Indiana University, will deliver the Aquinas College Lectures in Medical Psychology for 1960, Wednesday, February 24.

Doctor Nurnberger, chairman in the department of psychiatry of the Indiana University School of Medicine and director of the University's Institute of Psychiatric Research, will speak in the afternoon and again in the evening. A dinner in the college dining room will be served between the two lectures.

Dr. Nurnberger's afternoon lecture will be entitled "Sex and Psychotherapy: A Clarification," and the evening lecture will be on "The Major Manifestations of Mental and Emotional Disorders: A Guide to Rapid Appraisal."

All MSMS members are invited to these lectures.

**LAWRENCE REYNOLDS, M.D., HONORED.**—On February 5, at the Roosevelt Hotel in New York, the Gold Medal of the American College of Radiology will be bestowed on Dr. Lawrence Reynolds, Detroit, by unanimous action taken by the Board of Chancellors in recognition of "distinguished and extraordinary service to the American College of Radiology and the profession for which it stands." Dr. Reynolds has received the honorary degrees of Doctor of Laws, from the University of Alabama (1949) and the Wayne State University (1956). He is an honorary member of the Radiologic Societies of Germany, Italy and Columbia. He is Pancoast Lecturer (1942), Caldwell Lecturer (1944), Hickey Lecturer (1954), Past President of the American Roentgen Ray Society (1948), Gold Medalist of the Radiological Society of North America (1956) and now President of the American College of Radiology.

Contributions for this "News Briefs" department are invited from individual physicians, from county societies, and from other health organizations. Please direct your contributions to the Editor.

**NEW ORGANIZATION.**—William L. Bedwell, M.D., Detroit, is the president of the newly organized Detroit Society for Psychoanalytic Study. The organization of Wayne-Oakland area psychiatrists will study psychoanalytic theory and its usefulness for the technique of psychotherapy. Other officers are Bella M. Rabinovitch, M.D., Detroit, vice president; Clinton J. Mumby, M.D., Pontiac, secretary, and Norman R. Schakne, M.D., Pontiac, treasurer.

**SELECT EXECUTIVE.**—Lawrence J. Linck is the new executive vice president of the National Association for Mental Health, which has 800 state and local affiliates. The NAMH business address is 10 Columbus Circle, New York 17, New York.

**DONORS NEEDED.**—"Lack of adequate supply of blood of all types from local donors may soon become a limiting factor in carrying out heart surgery," states William W. Coon, M.D., University of Michigan assistant professor of surgery.

Growing demands for blood in modern surgical care have caused the U-M Medical Center to issue a strong appeal for professional donors. Patients at University Hospital use about 850 pints of blood each month, while the professional donor list totals only 500 people. Doctor Coon reports they must double or triple the present list as quickly as possible.

In addition to heart cases, other large individual users at U-M are persons having severe burns, internal bleeding, and brain operations.

**DEDICATE WAYNE BUILDING.**—Dedication of Wayne State University's new Cohn Memorial Building took place Wednesday, November 18. The Cohn Memorial Building will house the College of Nursing, the division of graduate instruction and research, and also the School of Social Work.

The Cohn Foundation provided one of the two grants through which the building was made possible; the other came from the Greater Detroit Hospital Fund.

**FOSTER COOPERATION.**—A top-level liaison committee has been formed between the American Medical Association and the American Nurses' Association to explore matters of mutual concern in the interest of improved health care.

**AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY.**—The next scheduled examinations (Part II), oral and clinical, for all candidates, will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from April 11 through 16, 1960. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates. Candidates who participated in the Part I examinations will be notified of their eligibility for the Part II examinations as

soon as possible. For information, write Robert L. Faulkner, M.D., Board Secretary, 2105 Adelbert Road, Cleveland 6, Ohio.

**RETIRED AS REAR ADMIRAL.**—Herman D. Scarney, M.D., chief of staff of William Beaumont Hospital, Royal Oak, has been placed on the retired list of the United States Navy Reserve with the rank of Rear Admiral.

H. D. Scarney, M. D.

Admiral Scarney completed over thirty years of service in the United States Navy and was active in the aviation arm of the Navy during World War II. His active duty included senior medical officer and chief flight surgeon at the Naval Air Station, Grosse Ile, and as senior medical officer and chief flight surgeon aboard the Aircraft Carrier *U.S.S. Cabot*. A member of the Wayne County Medical Society, Admiral Scarney is a past president of the Detroit Ophthalmological Society, and is affiliated with numerous other medical organizations.

**TO GIVE ADDRESS.**—Jerome W. Conn, M.D., Ann Arbor, will speak at the eighth postgraduate course in Diabetes and Basic Metabolic Problems, Los Angeles, January 20-21-22. He will discuss "Newer Diagnostic Methods in Diabetes."

**REPORTS ON STUDY.**—C. Thomas Flotte, M.D., University of Michigan Medical Center, reports, "We have learned from mummies that diseases of 3,000 years ago are essentially the same ones that are present today."

He cites an archaeologists's discovery of a mummy with a kidney abscess. Material from the abscess was taken to a laboratory "and the scientists were able to culture the same type of organism that will cause kidney infections at the present time."

**STUDIES IMMUNIZATION.**—The National Institutes of Health in Washington awarded V. K. Volk, M.D., Saginaw, a two-year grant in the amount of $49,772.00 or $24,886.00 per year, to carry on a study of immunization of infants against diphtheria, whooping cough, tetanus, and poliomyelitis. This study will be carried out in cooperation with the Michigan Department of Health, the School of Public Health, University of Michigan and Saginaw physicians.

The purpose of the study is to acquire a greater knowledge on the best method of immunization of infants against these diseases.

**CONFERENCE LEADER.**—William J. Burns, MSMS Executive Director, recently served as chairman of a general session and also moderator of a panel for the Professional Association Executives Division at the annual meeting of the American Society of Association Executives.

**TALKS AT DETROIT.**—Lewis Cohen, M.D., Detroit, presented an exhibit and a paper entitled "Electrovasography: Quantitative Diagnosis of Vascular Disorders" at the annual meeting of the Gerontological Society in Detroit, November 12 to 14, 1959.

**INVITE APPLICANTS.**—The University of Cincinnati Institute of Industrial Health offers graduate fellowships in industrial medicine. The Institute, a division in the College of Medicine, provides professional training for graduates of approved medical schools who have completed at least one year of internship. Requests for information should be addressed to: Secretary, Institute of Industrial Health, College of Medicine, Eden and Bethesda Avenues, Cincinnati 19, Ohio.

**JOHN ALEXANDER LECTURE.**—The third Annual John Alexander lecture was given at the University of Michigan Medical Center, November 12 by Michael E. DeBakey, M.D., chairman of the Department of Surgery, Baylor University College of Medicine, Houston, Texas.

The lectureship was established by the John Alexander Society in 1957 as a memorial to the former chief of thoracic surgery at the U-M. The Society—doctors who have trained in thoracic surgery under Dr. Alexander and his successor—invite a distinguished surgeon to present the lecture each year.

**RECEIVES HONORS.**—J. P. Gray, M.D., Detroit, was awarded the American Medical Writers Association Distinguished Service Award at the AMWA's 16th annual meeting in St. Louis.

Doctor Gray, one of six honored at the convention, was cited for "unusual and distinguished service to the medical profession."

**MATERNITY REPORT.**—According to a survey of group surgical insurance claims, the Health Insurance Institute reports that 87.5 per cent of the maternity claims were for normal deliveries and 3.9 per cent for cesarean sections. The survey also showed that 8.1 per cent ended unsuccessfully in miscarriages and the remainder were extrauterine pregnancies. The Institute report was based on a 1957 survey by the Society of Actuaries of more than 118,000 group surgical insurance claims.

**GETS NATIONAL POST.**—Edward C. Rosenow, Jr., M.D., Los Angeles, has been named executive director of the American College of Physicians. He will succeed Edward R. Loveland, who retired December 31, 1959, after thirty-four years as the executive secretary. Doctor Rosenow has been on the faculty of the University of Southern California School of Medicine, and has been the executive director of the Los Angeles County Medical Association since 1957. His varied activities have included editor of *Audio-*

*Digest* since its inception in 1954, and past president of the Los Angeles County Medical Association.

**PRESENTS TALKS.**—M. K. Newman, M.D., Detroit, participated in the following conferences and gave the following talks: (1) "Rehabilitation Requirements in Terms of Workmen's Compensation Laws," at a combined conference of the National Rehabilitation Association and the Group Health Association, Washington, D. C., October 9; (2) "Diagnosis and Management of Circulatory Impairment of the Lower Extremities," before the State Meeting of the Michigan Chiropody Society, Statler-Hilton Hotel, October 31; (3) "Current Aspects of Rehabilitation in Chronic Illness and Disability," before the Oakland County Department of Health, Pontiac, on October 23; and (4) "A Community Approach to Rehabilitation" before the Michigan Welfare League, Grand Rapids, November 4.

**GOLDEN JUBILEE.**—The 50th anniversary of American Red Cross First Aid Service will be observed throughout 1960 and with special emphasis at the national convention in Kansas City next May. The Service was officially inaugurated by Red Cross January 1, 1910, during which year the first textbook on first aid was published. Since that time, the Red Cross is the only organization to offer continually a nationwide first aid training program. Since 1910, some 21,000,000 certificates for Red Cross first aid training have been granted. Certificates of Merit for saving lives have been issued to 2,200 persons during the past seventeen years. Countless other lives have been spared by this vital Red Cross program.

**SPEAKS IN GUATEMALA.**—H. Marvin Pollard, M.D., Ann Arbor, gave two talks at the National Medical Congress of Guatemala, November 25 to 27 at Guatemala City. Doctor Pollard also visited the Nutrition Hospital in Mexico City during his trip.

**BOOST PENBERTHY FUND.**—The Wayne State University Board of Governors at its November meeting accepted a gift of $7,713.21 from the estate of the late William A. Spitzley, M.D., for the Grover C. Penberthy Research Fund in the College of Medicine.

**BIG BUSINESS.**—In the fourteen-year period since the end of World War II, the National Library of Medicine has had 172,360 volumes bound in outside binderies, and has bound, mended or repaired 77,068 additional volumes in its own shop, for a total of a quarter of a million volumes, or almost fifty for every calendar day during the period.

**HONOR U-M ALUMUS.**—Among four University of Michigan alumni who received Outstanding Achievement Awards Saturday night, November 21, was Charles W. Shilling, M.D., deputy director of the Division of Biology and Medicine of the Atomic Energy Commission, Washington, D. C. Doctor Schilling was born Sept. 21, 1901 at Upland, Indiana, and he joined the United States Navy Medical Corps immediately after receiving his M.D. degree in 1927. He retired from the Navy in 1955 to assume his present post with the Atomic Energy Commission.

**OFFER ASSISTANCE.**—Thirty scholarships providing tuition, room and board at the Midwest Institute of Alcohol Studies at Madison, June 13 to 17 and another fifteen scholarships to the Yale School of Alcohol Studies, June 26 to July 22, will be granted by the Michigan State Board of Alcoholism. Applications may be requested from Ralph Daniel, director, State Board of Alcoholism, 230 N. Grand, Lansing.

**PRICE REDUCTION.**—The Upjohn Company has announced a reduction in the price of its oral antidiabetic agent Orinase. The reduction, which is effective immediately, should result in a saving to patients of approximately 50 cents a bottle, or a cent a tablet.

**MEDICALLY IMPORTANT MOSQUITOES.**—"Mosquitoes of Medical Importance," by Richard R. Foote and David R. Cook, a handbook, will enable both military and civilian entomologists, especially those concerned with public health, to identify mosquitoes in any part of the world. Copies of "Mosquitoes of Medical Importance" may be obtained without charge from the Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, Washington 25, D. C.

**YAMASAKI HONORED.**—Minoru Yamasaki, architect who designed the new Michigan State Medical Society building, was awarded the 1959 Gold Medal of the Detroit Chapter, American Institute of Architects.

## COMING MEETINGS

The Industrial Medical Association will hold its forty-fifth annual convention in the new War Memorial Auditorium, Rochester, New York, April 26-28, 1960.

The sixty-seventh Annual Conference of the Association of Military Surgeons will be held at the Mayflower Hotel, Washington, D. C., October 31, November 1 and 2, 1960.

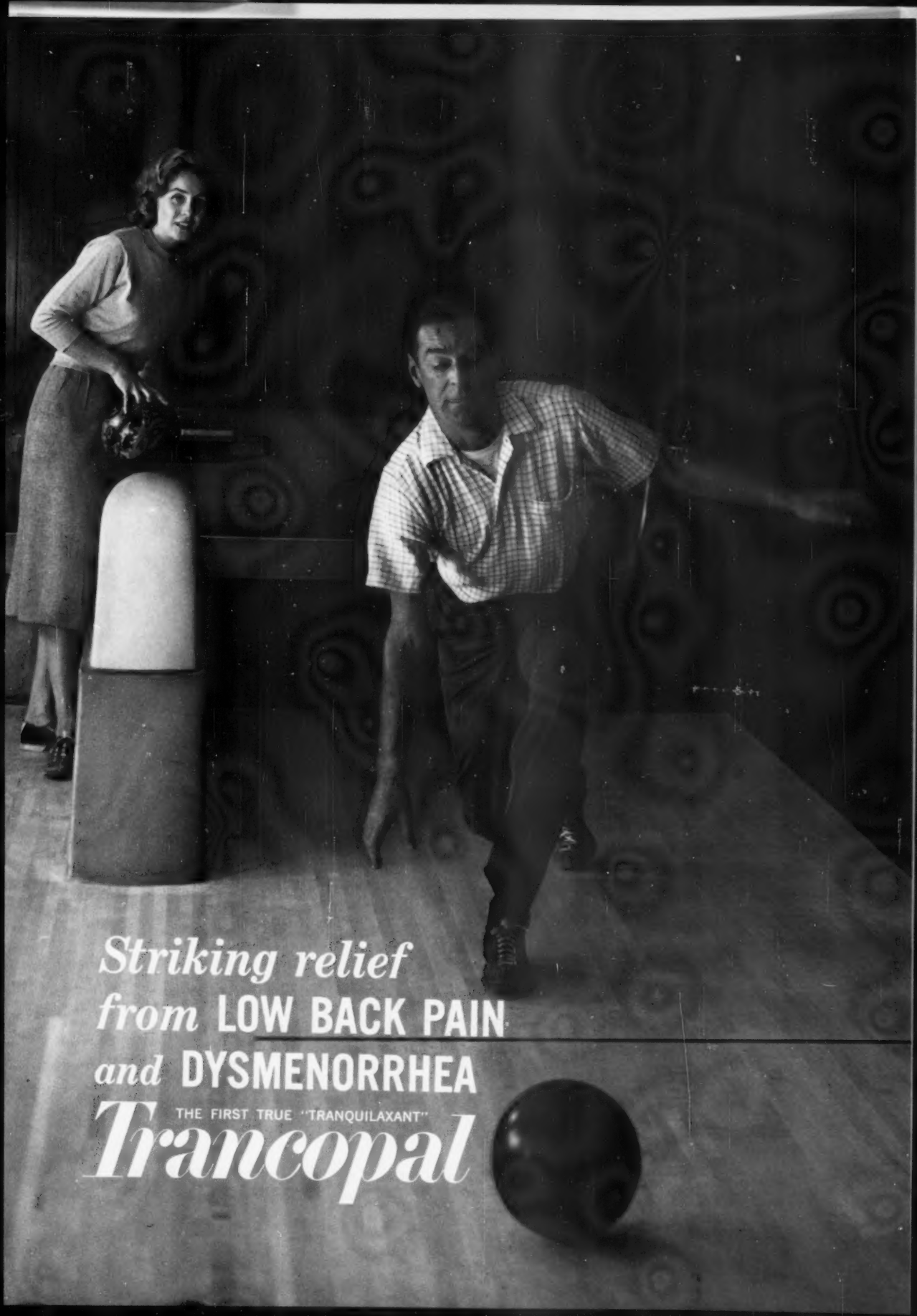
The American Otorhinologic Society for Plastic Surgery will meet at Miami Beach, March 6 to 13, 1960.

The American College of Surgeons will conduct a four-day Session for Surgeons and Nurses in Boston, February 29, March 1, 2, 3, 1960.

The American College of Radiology will hold its annual session in New Orleans, Louisiana, February 3 to 6, 1960.

The American Radiation Society will meet in San Juan, Puerto Rico, March 17 to 19, 1960.

The Third International Congress of Physical Medicine will be held August 21 to 26, 1960, inclusive, at The Mayflower, Washington, D. C. For information write: Dorothea C. Augustin, Executive Secretary, Third International Congress of Physical Medicine, 30 N. Michigan Avenue, Chicago 2. Illinois.


Striking relief
from LOW BACK PAIN
and DYSMENORRHEA
THE FIRST TRUE "TRANQUILAXANT"
Trancopal

# Here is what you can expect when you prescribe

## for dysmenorrhea

*and premenstrual tension*

## Case Profile*

A 28-year-old married woman, a secretary in a booking agency, complained of severe and consistent pain and cramps in the abdomen during her menstrual periods. Psychologically, she described the first two days as "climbing the walls." Menarche occurred at age 13. She has a regular twenty-eight day menstrual cycle and a four day menstrual period.

Trancopal was given in a dose of 100 mg. four times a day for the first two days of the four day period. In addition to the relief of the dysmenorrhea she also noticed disappearance of a "bloated feeling" that had previously annoyed her. She has now been treated with Trancopal for one and one-half years with excellent results. Other medication, such as codeine or aspirin with codeine, had relieved the pain, but the patient had had to stay home. Because her father is a physician, many commercial preparations had been tried prior to Trancopal, but no success had been achieved.

Before taking Trancopal this patient missed one day of work every month. For the past year and a half she has not missed a day because of dysmenorrhea.

THE FIRST TRUE "TRANQUILAXANT"

# Trancopal®

## for low back pain

## Case Profile*

A 42-year-old truck driver and mover injured his back while moving a piano. The pain radiated from the sacral region down to the region of the Achilles tendon on the right side. X-rays for ruptured disc revealed nothing pertinent. The day of the injury he was given Trancopal immediately after the physical examination. Although 100 to 200 mg. three times a day were prescribed, the patient on his own responsibility increased the dosage of Trancopal to 400 mg. three times a day. This dosage was continued for three days and then gradually reduced over a ten day period. During this time, the patient continued to drive his truck. The muscle spasm was completely controlled and no apparent side effects were noted.

For the past six months, the patient has continued to take Trancopal 100 to 200 mg. as needed for muscle spasm, particularly during strenuous days.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

Turn page for complete listings of Indications and Dosage.

THE FIRST TRUE "TRANQUILAXANT"

# Trancopal

## potent MUSCLE RELAXANT

## effective TRANQUILIZER

- In musculoskeletal disorders, effective in 91 per cent of patients.[1]
- In anxiety and tension states, effective in 89 per cent of patients.[1]
- Low incidence of side effects (2.3 per cent of patients). Blood pressure, pulse rate, respiration and digestive processes are unaffected by therapeutic dosage. It does not affect the hematopoietic system or liver and kidney function.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.

### Indications [1-6]

**Musculoskeletal:**

Low back pain (lumbago, etc.)
Neck pain (torticollis)
Bursitis
Rheumatoid arthritis
Osteoarthritis
Disc syndrome
Fibrositis
Ankle sprain, tennis elbow
Myositis
Postoperative muscle spasm

**Psychogenic:**

Anxiety and tension states
Dysmenorrhea
Premenstrual tension
Asthma
Angina pectoris
Alcoholism

### Now available in two strengths:

Trancopal Caplets®,
100 mg. (peach colored, scored), bottles of 100.

NEW STRENGTH ▶

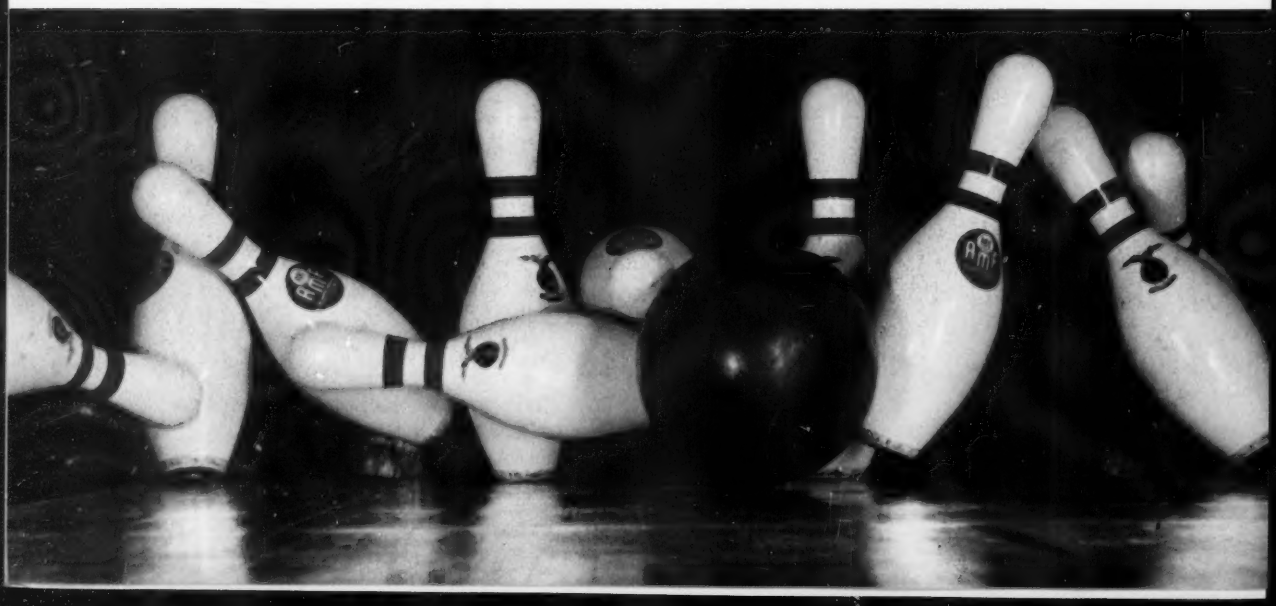
Trancopal Caplets,
200 mg. (green colored, scored), bottles of 100.

*Dosage:* Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

Winthrop LABORATORIES
New York 18, N. Y.

*References:* 1. Collective Study, Department of Medical Research, Winthrop Laboratories. 2. Lichtman, A. L.: New developments in muscle relaxant therapy, *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 3. Lichtman, A. L.: Relief of muscle spasm with a new central muscle relaxant, chlormezanone (Trancopal), Scientific Exhibit, Meeting of the International College of Surgeons, Miami Beach, Fla., Jan. 4-7, 1959. 4. Ganz, S. E.: Clinical evaluation of a new muscle relaxant (chlormethazanone), *J. Indiana M. A.* 52:1134, July, 1959. 5. Mullin, W. G., and Epifano, Leonard: Chlormezanone, a tranquilizing agent with potent skeletal muscle relaxant properties, *Am. Pract. Digest Treat.* 10:1743, Oct., 1959. 6. Shanaphy, J. F.: Chlormezanone (Trancopal) in the treatment of dysmenorrhea: a preliminary report, *Current Therap. Res.* 1:59, Oct., 1959.





**DRUG FIRMS WIN.**—Five major drug firms have been acquitted of charges that they rigged the price of Salk anti-polio vaccine. The companies hailed the decision as "vindication" and "exoneration."

Federal Judge Phillip Forman ruled yesterday that the government had not shown a definite conspiracy through its evidence, and he saw no reason to let the case go on to add the defense testimony. He granted defense motions for directed verdicts of acquittal after a two hour and forty-five minute summary of the evidence. The jury had been exused. Thus the all-male jury, which had sat through five weeks of prosecution arguments and testimony, never heard the end of the case.

Lewis Bernstein, the government's prosecuting attorney, said the dismissal cannot be appealed since the charges were criminal in nature. The companies could have been fined $200,000 each if found guilty.

Acquitted were Eli Lilly & Co., Indianapolis, Indiana; Parke-Davis company, Detroit; Wyeth Laboratories of American Home Products corporation, New York; Pitman-Moore division, Allied Laboratories, Kansas City, Missouri; and Merck Sharp & Dohme Division, Merck, Inc., Rahway, New Jersey.

The government contended the companies had a hold-the-line agreement on prices to federal and state agencies. They sold $53,000,000 in vaccine to the U.S. government from 1955 through 1957, and, generally, bids on contracts were identical.—*Lansing State Journal*, Dec. 1, 1959.

## MITRAL AND AORTIC STENOSIS

*(Continued from Page 103)*

they have reached the point of actual failure, a satisfactory degree of correction can be accomplished without an unacceptable risk. On the other hand, if these patients are presented for operation only after they have experienced bouts of severe failure, the risk is high owing to the fact that the ventricle is exhausted and the changes in the aortic valve are so extensive that simple commissurotomy (either by open or closed methods) does not produce a degree of functional correction which is satisfactory. In our own practice, we have developed a technique of increasing the coronary artery flow and maintaining the central blood pressure just before and during transventricular aortic valvulotomy. This technique consists in construction of the descending aorta to maintain the proximal pressure. This has materially reduced the incidence of ventricular arrythmias during the operation.

An ideal not yet attained, but entirely feasible, with the modern pump oxygenators is that one day we will be able to remove the aortic valve *in toto* and replace it with a dependable prosthesis.

# IN MEMORIAM

**GEORGE H. BAERT, M.D.,** eighty-nine, Grand Rapids physician for sixty-one years, died November 5, 1959.

Doctor Baert was born in Zeeland. He was graduated from Hope College in 1888 and received a degree in pharmaceutical chemistry from the University of Michigan in 1890. After a year at Purdue University as a chemistry teacher, he entered the University of Pennsylvania Medical School in 1891 and was graduated in 1893.

He opened practice the same year in the Kendall Professional Building, Grand Rapids, where he maintained offices until his retirement. In his early years of practice he served as pathologist at Blodgett Memorial Hospital.

He was a member of the East Congregational Church, York Lodge No. 410 F.&A.M. and DeWitt Clinton Consistory and for many years was active in area art groups as an oil painter.

In 1947, Doctor Baert was the recipient of an MSMS Fifty-Year Award, an honor for having practiced medicine for half a century.

**JOHN D. McKINNON, M.D.,** eighty, Highland Park physician for thirty-eight years, died November 6, 1959.

Doctor McKinnon was graduated from the University of Michigan Medical School in 1908, and had practiced in Calumet before moving to Highland Park.

A former head of the obstetrics department at Highland Park General, he was a member of Calumet Lodge No. 271, F.&A.M., Calumet Chapter 153, Royal Arch Masons and Montrose Commandery 38, Knights Templar.

**OLIN EARL PARMELEE, M.D.,** eighty-five, Lambertville community doctor for over fifty years, died October 21, 1959.

Born on a farm near Hillsdale, Doctor Parmelee worked as a farm hand and on a railroad as a young man and later became a bellboy in a Chicago hotel.

His early interest in the medical profession prompted him to become a male nurse in a Chicago hospital before he enrolled in Harvey College at Chicago.

Graduating from the University of Illinois Medical School in 1905, he interned at a Chicago hospital and in 1906 set up his practice in Lambertville.

He was a member of the Methodist church, IOOF and various Masonic orders.

**PHILLIP H. PAYE, M.D.,** fifty, chief of radiology at Cadillac's Mercy Hospital and Manistee Community Hospital, died November 6, 1959.

A native of Grosse Pointe, Doctor Paye was a graduate of the University of Detroit High School and St. Louis University College of Medicine. He took advanced training at the Detroit Memorial Hospital and later joined the United States Public Health Service at Washington, D. C.

He served in the Army medical corps in World War II, advancing to the rank of lientenant colonel in charge of x-ray and pathology at the Wichita, Kansas, veterans administration hospital.

Doctor Paye was a member of St. Ann's Catholic church, Cadillac, the Elks club, the American Radiological society and was a director of Dirkes Industries of Detroit.

## *Medical Authors*

F. BRUCE FRALICK, M.D., Ann Arbor, is the author of an article entitled "Surgical Anatomy, Physiology, and the Three Main Operative Approaches," a part of a symposium: Ptosis Complications, which was presented as a special program of the Committee on Reconstructive Plastic Surgery: Ophthalmology at the Sixty-third Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 12 to 17, 1958, Chicago, and published in *Transactions*, American Academy of Ophthalmology and Otolaryngology, September-October, 1959.

ARAN S. JOHNSON, M.D., Detroit, is the author of an article entitled "Surgery in Acquired and Congenital Coronary Insufficiency," published in *Clinical Medicine*, October, 1959.

Z. E. TAHERI, M.D., F.A.C.S., F.I.C.S., D.A.B., Bay City, is the author of an article entitled "Urevert in Cranial Trauma and Brain Surgery," published in *the Journal of the International College of Surgeons*, October, 1959.

CLARENCE E. RUPE, M.D., and STEWART N. NICKEL, M.D., Detroit, are the authors of an article entitled "New Clinical Concept of Systemic Lupus Erythematosus," published in the *Journal of the American Medical Association*, October 24, 1959.

EARL J. HALLIGAN, M.D., Jersey City, New Jersey, and FOUAD A. RABIAH, M.D., Highland Park, are the authors of an article entitled "Primary Idiopathic Segmental Infarction of the Greater Omentum," published in *A.M.A. Archives of Surgery*, November, 1959.

JEROME POLLACK, M.D., Detroit, is the author of an article entitled "Opinion Survey and Relative Value Study," published in the June issue of the *Journal of the Michigan State Medical Society*, and reprinted in *Connecticut Medicine*, October, 1959.

JOHN W. HENDERSON, M.D., Ann Arbor, is the author of an article entitled "Neuro-Ophthalmology," published in *A.M.A. Archives of Surgery*, November, 1959.

HAROLD F. FALLS, M.D., Ann Arbor, is the author of an article entitled "Manifestations of the Chronic Renal Tubular Insufficiency Symptoms," in *A.M.A. Archives of Ophthalmology*, August, 1959.

C. B. ROLAND, M.D., Lansing, is the author of an original article, "Pheochromocytoma in Pregnancy," which appeared in the *Journal of the American Medical Association*, November 28, 1959.

I. A. SCIME, M.D., and E. J. TALLANT, M.D., Detroit, are authors of an original article, "Tetanus-Like Reactions to Prochlorperazine (Compazine)," which appeared in the *Journal of the American Medical Association*, November 28, 1959.

JOHN G. REID, M.D., is the author of an article entitled "Osteochondritis Desiccans," presented before the Detroit Academy of Medicine, December, 1958, and published in *Harper Hospital Bulletin*, September-October, 1959.

C. C. HERRINGTON, M.D., and C. R. REINERS, M.D., Detroit, are the authors of an article entitled "The Management of Bile Duct Strictures," published in *Harper Hospital Bulletin*, September-October, 1959.

HUBERT U. WAGGENER, M.D., JAMES P. MULDOON, M.D., and J. RICHARD HEATON, M.D., Grand Rapids, are the authors of an article entitled "Asymptomatic Tuberculous Enteritis Simulating Carcinoma of the Cecum," published in the *Journal of the American Medical Association*, November 7, 1959.

B. F. MC CABE, M.D., and MERELE LAWRENCE, Ph.D., Ann Arbor, are authors of an article entitled "Inner-Ear Mechanics and Deafness," published in the *Journal of the American Medical Association*, December 5, 1959.

R. A. STRAFFON, M.D., and A. J. COPPRIDGE, M.D., Ann Arbor, are authors of an article entitled "Respiratory Paralysis and Severe Potassium Depletion after Ureterosigmoidostomy," published in the *Journal of the American Medical Association*, September 12, 1959.

JOHN M. HAMMER, M.D., PATRICK H. SEAY, Ph.D., RICHARD L. JOHNSTON, D.V.M., Kalamazoo, EDWARD J. HILL, M.D., FRANK H. PRUST, M.D., and RUTH J. CAMPBELL, Detroit, are the authors of an article entitled "The Effect of Antiperistaltic Bowel Segments on Intestinal Emptying Time," presented at the seventh annual meeting of the Michigan Chapter of the American College of Surgeons, Detroit, March 10, 1959, and published in *AMA Archives of Surgery*, October, 1959.

GEORGE L. WALDBOTT, M.D., Detroit, is the author of an article entitled "'Constitutional' Allergic Reactions and Their Prevention," published in the *Journal of the American Medical Association*, October 31, 1959.

J. MARTIN MILLER, M.D., ROBERT C. HORN, M.D., and MELVIN A. BLOCK, M.D., Detroit, are the authors of an article entitled "The Increasing Incidence of Carcinoma of the Thyroid in a Surgical Practice," published in the *Journal of the American Medical Association*, October 31, 1959.

Z. STEPHEN BOHN, M.D., Detroit, is the author of an article entitled "Morbid Changes in Mental Deficiency, the Experience of 28 Years with a Large Colony for the Mentally Defective," published in *Harper Hospital Bulletin*, September-October, 1959.

# The Doctor's Library

*Acknowledgments of all books received will be made in this column, and this will be deemed by us as full compensation to those sending them. A selection will be made for review, as expedient.*

NUTRITION AND ATHEROSCLEROSIS. By Louis N. Katz, M.D., Director, Cardiovascular Department, Medical Research Institute Michael Reese Hospital; and Professorial Lecturer in Physiology, University of Chicago, Chicago, Illinois. Jeremiah Stamler, M.D. Previously Assistant Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois, and Established Investigator of the American Heart Association; Presently Director, Heart Disease Control Program, Chicago; Board of Health, Chicago, Illinois. Ruth Pick, M.D., Assistant Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois, and Established Investigator of the American Heart Association. 67 Illustrations. Philadelphia: Lea & Febiger, 1958. Price, $5.00.

This small book of something over 100 pages is a concise review of the literature pertaining to the rapidly moving field of research in atherosclerosis, particularly emphasizing the relation of the disease to nutrition. Data from personal studies of one of the authors is also presented. Although other endogenous factors in the development of atherosclerosis are carefully evaluated, diet assumes the key role in this dissertation.

Various proposed prophylactic and therapeutic regimens are critically reviewed in the light of the research of the last ten years. The author presents an interim approach to this as yet unsettled question of the best means of prevention and management with specific practical recommendations. An extensive bibliography of the literature particularly since 1953 is included, together with many illustrative charts and graphs.

It is recommended reading for the cardiologist, the internist, nutrition experts, and the well informed general practitioner of medicine as well as the young physician approaching the "dangerous age" with a thought to his personal welfare.

R.W.B.

SYNOPSIS OF OPHTHALMOLOGY. By William H. Havener, B.A., M.D., M.S. (Ophth.) Professor and Chairman, Department of Ophthalmology, Ohio State University; Member of Attending Staff, University Hospital, Columbus, Ohio; Consultant, Veterans Hospital, Dayton, Ohio; Member of Consulting Staff, Children's Hospital and Mount Carmel Hospital, Columbus, Ohio. 189 illustrations. St. Louis: The C. V. Mosby Company, 1959. Price, $6.75.

Havener's Synopsis of Ophthalmology is exactly what the title implies, but it is the most complete synopsis one could ask for. The introductory parts give the equipment and facilities necessary for an ophthalmological office. The discussion and description of diseases are clear but short and are illustrated with well-selected pictures sufficiently large to illustrate the subject. It is pocket size with round corners—a very handy reference book. It will be useful to students, both in general medicine and in ophthalmology.

CLINICAL ORTHOPAEDICS. By Anthony F. DePalma, Editor-in-Chief, with the assistance of the Associate Editors, the Board of Advisory Editors, and the Board of Corresponding Editors. Number 14, Summer, 1959. Albert B. Ferguson, Jr., Guest Editor. Philadelphia and Montreal: J. B. Lippincott Company, 1959. Price $7.50.

This volume, like the earlier ones, is divided into a lead section dealing with a given subject or area of discussion, a second section on items of general orthopedic interest, and a final section on scattered subjects, often involving uncommon, but annoying, problems.

The first section, involving recent advances in orthopedic surgery in infancy and childhood, in itself makes the modest price of the book worthwhile. In particular, the article on juvenile amputees by Drs. Frantz and Aitken is "must" reading for those not already familiar with their stature in this field.

The general section has two particularly good reviews, one of the role of surgical procedures in the treatment of arthritis, and the other an excellent discussion of the painful coccyx.

The last section presents no pearls this time, but the lead section, as always, continues to make this volume a highly desirable addition to its predecessors in the series.

R.H.A.

DIAGNOSIS AND TREATMENT OF MENSTRUAL DISORDERS AND STERILITY. Fourth Edition. By S. Leon Isreal, M.D., Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Chief Gynecologist, Graduate Hospital; Gynecologist and Obstetrician, Pennsylvania Hospital, Philadelphia. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1959. Price, $15.00.

This volume contains the completely rewritten material of the previous three volumes with the addition of three new chapters dealing with the role of androgens, thyroid and adrenal cortex in menstrual disorders.

The problems arising in everyday practice are emphasized and discussed from the clinician's point of view. At the end of each chapter, there is an excellent list of references for those who want more detail.

One of the highlights of this book is the discussion of sterility. It includes not only the female factors but the male factors as well.

This book is very detailed and introduces many new concepts. The chapters on recurrent abortion and artificial insemination are up to date and all-inclusive. This book is very well written and is of special value to the busy clinician as well as to the student.

J.R.P.

THE CIBA COLLECTION OF MEDICAL ILLUSTRATIONS. Volume 3. A Compilation of Paintings on the Normal and Pathologic Anatomy of the DIGESTIVE SYSTEM. Part I. Upper Digestive Tract. Prepared by Frank H. Netter, M.D. Edited by Ernst Oppenheimer, M.D. Commissioned and published by CIBA, 1959. Price, $12.50.

Part I of Volume 3 is concerned with the Digestive System. It is a magnificent anatomical exposition of the digestive tract. Its many pages include color pictures with extremely fine detail including the anatomy of the mouth and pharynx, teeth, tongue, glands. It also includes anatomy of the esophagus, stomach, duodenum, functional and diagnostic aspects of the upper digestive tract, diseases of the mouth and pharynx, the esophagus, and diseases of the stomach and duodenum. These pictures give the anatomy of the muscles, the arteries, the veins, the nerves, the lymphatic system including also, where applicable, microscopic sections showing the various areas. There are 172 full color plates. The descriptions are clear and lucid. The reviewer is greatly pleased with the book, which compares well with its predecessors.

SYNOPSIS OF GYNECOLOGY. Fifth Edition. By Robert James Crossen, M.D., Associate Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, St. Louis, Mo.; Daniel Winston Beacham, M.D., Assistant Professor of Clinical Obstetrics and Gynecology, Tulane University School of Medicine, New Orleans, La.; Woodard Davis Beacham, M.D., Professor of Clinical Obstetrics and Gynecology, Tulane University School of Medicine, New Orleans, La. St. Louis: C. V. Mosby Company, 1959. Price, $6.50.

This hand book is one of the most complete synopsis of the subject of Gynecology written today. It is an important supplement to the standard texts.

The chapter on gynecologic examination and diagnosis is outstanding because of its comprehensive text and excellent accompanying charts and diagrams.

This edition is completely rewritten and new chapters have been added—one on endometriosis and one on the complications of pregnancy. Other subject material has been reorganized and brought up to date. Laboratory work and associated clinical findings are correlated with the history for the purpose of diagnosis.

This book is of great value to all practitioners in all fields of medicine.

J.R.P.

## BOOKS RECEIVED

THE FAMILY MEDICAL ENCYCLOPEDIA. By Justus J. Schifferes, Ph.D. Illustrated by Louise Bush, Ph.D. A Health Education Council Book. Boston and Toronto: Little, Brown & Co., 1959. Price, $4.95.

BONE TUMORS. By Louis Lichtenstein, M.D., Chief Pathologist, General Medical and Surgical Hospital, Veterans Administration Center, Los Angeles; Fellow, New York Academy of Medicine; Professor Extraordinario, National University of Mexico; Consultant in Bone Tumors, Tumor Tissue Registry of California Medical Association Cancer Commission; Consultant in Pathology, Los Angeles County Hospital; Consultant, City of Hope Medical Center. 220 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1959. Price, $12.00.

PATIENT CARE AND SPECIAL PROCEDURE IN X-RAY TECHNOLOGY. By Carol Hocking Vennes, R.N., B.S., formerly Surgical Supervisor and Clinical Instructor, University of Minnesota Hospitals, Minneapolis, Minnesota, and John C. Watson, R.T., Director of Courses in X-Ray Technology, University of Minnesota Hospitals, Minneapolis, Minnesota. Illustrated. St. Louis: The C. V. Mosby Company, 1959. Price, $5.75.

THE TREATMENT OF DIABETES MELLITUS. Tenth edition, revised. By Elliott P. Joslin, Howard F. Root, Priscilla White, and Alexander Marble. Illustrated. Philadelphia: Lea & Febiger, 1959. Price, $16.50.

501 QUESTIONS AND ANSWERS IN ANATOMY. By Stanley D. Miroyiannis, B.S., M.A., Ph.D., F.A.A.A.S., F.I.A.S., Professor of Anatomy and Chairman of the Department, Still College. Formerly: Lecturer in Comparative History, Boston University; Professor of Vertebrate Anatomy and Chairman of the Department of Biology, Northeastern University; Professorial Lecturer in Mammalian Anatomy, Graduate School, Massachusetts College of Pharmacy; Professor of Gross Anatomy and Chairman of the Department, The New England Institute of Anatomy; Major, The Medical Service Corps, Staff and Faculty, 373rd General Hospital Unit; Lt. Colonel, Staff and Faculty 5904th Medical Department, 5904 School, USAR. Presently: Lt. Colonel, The Medical Service Corps, USAR; Professor of Human Gross Anatomy and Chairman of the Department, Still College, Des Moines, Iowa. With an introduction by Ernest V. Enzmann, Ph.D., Associate Professor of Histology and Embryology. Still College. New York, Washington, Hollywood: Vantage Press, 1959. Price, $5.00.

AMINO ACIDS AND PEPTIDES WITH ANTIMETABOLIC ACTIVITY. Symposium Editors for the Ciba Foundation, G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. 28 illustrations. Boston: Little, Brown and Company, 1959. Price, $8.75.

THE PLASMA PROTEINS. Clinical Significance. By Paul G. Weil, B.A., M.D.C.M., M.Sc., Ph.D., Director, Transfusion Service and Assistant Physician, Royal Victoria Hospital; Lecturer in Medicine, McGill University; Consultant in Medicine, Queen Mary Veterans and Grace Dart Hospitals; Consultant in Transfusion. Queen Elizabeth and Royal Edward Laurentian Hospitals. Philadelphia and Montreal. J. B. Lippincott Company, 1959. Price, $3.50.

NUTRITION AND ATHEROSCLEROSIS. By Louis N. Katz, M.D., Director, Cardiovascular Department Medical Research Institute, Michael Reese Hospital; Professorial Lecturer in Physiology, University of Chicago; Chicago, Illinois. Jeremiah Stamler, M.D., previously Assistant Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois, and Established Investigator of the American Heart Association; presently Director, Heart Disease Control Program, Chicago; Board of Health, Chicago, Illinois. Ruth Pick, M.D., Assistant Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois, and Established Investigator of the American Heart Association. 67 illustrations. Philadelphia: Lea & Febiger, 1958. Price, $5.00.

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*Source:* Traisman, H. S.; Boehm, J. J., and Newcomb, A. L.: Diabetes *8*:289, 1959.

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### DIABETES MELLITUS AT AGES 1 TO 5

Order of Frequency of Presenting Symptoms in 110 Patients

| Symptoms | No. of Patients | Per cent of total group |
|---|---|---|
| Polyuria | 93 | 84.5 |
| Polydipsia | 89 | 81.0 |
| Weight loss | 47 | 42.7 |
| Polyphagia | 28 | 25.4 |
| Anorexia | 16 | 14.5 |
| Lethargy | 14 | 12.7 |
| Enuresis | 7 | 6.4 |
| Vomiting | 5 | 4.5 |
| Irritability | 3 | 2.7 |
| "Craving for sweets" | 3 | 2.7 |
| "Sticky diaper" | 3 | 2.7 |
| "Strong odor to urine" | 2 | 1.8 |
| Glycosuria | 2 | 1.8 |
| Hypoglycemia | 2 | 1.8 |
| Personality change | 1 | 0.9 |
| Boils | 1 | 0.9 |
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